MAY 2013
STAFF REPORT to the NIDA DIRECTOR

TABLE OF CONTENTS

RESEARCH FINDINGS

BASIC AND BEHAVIORAL RESEARCH

Upregulation Of Nerve Growth Factor In Central Amygdala Increases Sensitivity To Opioid Reward The rewarding properties of opioids are essential driving force for compulsive drug-seeking and drug-taking behaviors in the development of opioid-mediated drug addiction. Prior drug use enhances sensitivity to the rewarding effects of subsequently used drugs, increasing vulnerability to relapse. The molecular mechanisms underlying this reward sensitization are still unclear. The authors report here that morphine that induced reward sensitization, as demonstrated by reinstatement of the behavior of conditioned place preference (CPP) with sub-threshold priming morphine, epigenetically upregulated the output activity of Ngf encoding the nerve growth factor (NGF) by increasing histone H4 acetylation in the rat central nucleus of the amygdala (CeA). NGF locally infused into the CeA mimicked the morphine effect in inducing new functional delta-opioid receptor (DOR) that was required for the reward sensitization, and morphine-induced reward sensitization was inhibited by blocking NGF receptor signaling in the CeA. Histone deacetylase inhibitors that increased the acetylation level at the Ngf promoter and NGF expression in the CeA also induced reward sensitization in a CeA NGF signaling- and DOR-dependent manner. Furthermore, CeA-applied NGF substituted prior morphine to induce reward sensitization in naive rats and also substituted priming morphine to reinstate the CPP induced by prior morphine. Thus, epigenetic upregulation of NGF activity in the CeA may promote the behavior of opioid reward and increase the sensitivity to the rewarding effect of subsequent opioids, a potentially important mechanism in drug addiction. Bie B, Wang Y, Cai YQ, Zhang Z, Hou YY, Pan ZZ. Upregulation of nerve growth factor in central amygdala increases sensitivity to opioid reward. Neuropsycho-pharmacology 2012; 37(13): 2780-2788.

Class I HDAC Inhibition Blocks Cocaine-Induced Plasticity By Targeted Changes In Histone Methylation Induction of histone acetylation in the nucleus accumbens (NAc), a key brain reward region, promotes cocaine-induced alterations in gene expression. Histone deacetylases (HDACs) tightly regulate the acetylation of histone tails, but little is known about the functional specificity of different HDAC isoforms in the development and maintenance of cocaine-induced plasticity, and previous studies of HDAC inhibitors report conflicting effects on cocaine-elicited behavioral adaptations. Here the authors demonstrate that specific and prolonged blockade of HDAC1 in NAc of mice increased global levels of histone acetylation, but also induced repressive histone methylation and antagonized cocaine-induced changes in behavior, an effect mediated in part through a chromatin-mediated suppression of $GABA_A$ receptor subunit expression and inhibitory tone on NAc neurons. These findings suggest a new mechanism by which prolonged and selective HDAC inhibition can alter behavioral and molecular adaptations to cocaine and inform the development of therapeutics for cocaine addiction. Kennedy PJ, Feng J, Robison AJ, Maze I, Badimon A, Mouzon E, Chaudhury D, Damez-Werno DM, Haggarty SJ, Han MH, Bassel-Duby R, Olson EN, Nestler EJ Class I HDAC inhibition blocks cocaine-induced plasticity by targeted changes in histone methylation. Nat Neurosci. 2013 Mar 10. doi: 10.1038/nn.3354. [Epub ahead of print].

ABHD12 Controls Brain Lysophosphatidylserine Pathways That Are Deregulated In A Murine Model Of The Neurodegenerative Disease PHARC Advances in human genetics are leading to the discovery of new disease-causing mutations at a remarkable rate. Many such mutations, however, occur in genes that encode for proteins of unknown function, which limits our molecular understanding of, and ability to devise treatments for, human disease. Here, the authors use untargeted metabolomics combined with a genetic mouse model to determine that the poorly characterized serine hydrolase α/β-hydrolase domain-containing (ABHD)12, mutations in which cause the human neurodegenerative disorder PHARC (polyneuropathy, hearing loss, ataxia, retinosis pigmentosa, and cataract), is a principal lysophosphatidylserine (LPS) lipase in the mammalian brain. ABHD12(-/-) mice display massive increases in a rare set of very long chain LPS lipids that have been previously reported as Toll-like receptor 2 activators. The authors confirm that recombinant ABHD12 protein exhibits robust LPS lipase activity, which is also substantially reduced in ABHD12(-/-) brain tissue. Notably, elevations in brain LPS lipids in ABHD12(-/-) mice occur early in life (2-6 mo) and are followed by age-dependent increases in microglial activation and auditory and motor defects that resemble the behavioral phenotypes of human PHARC patients. Taken together, these data provide a molecular model for PHARC, where disruption of ABHD12 causes deregulated LPS metabolism and the accumulation of proinflammatory lipids that promote microglial and neurobehavioral abnormalities. Blankman JL, Long JZ, Trauger SA, Siuzdak G, Cravatt BF. ABHD12 controls brain lysophosphatidylserine pathways that are deregulated in a murine model of the neurodegenerative disease PHARC. Proc Natl Acad Sci U S A 2013; 110(4): 1500-1505.

Prolonged High Fat Diet Reduces Dopamine Reuptake without Altering DAT Gene Expression The development of diet-induced obesity (DIO) can potently alter multiple aspects of dopamine signaling, including dopamine transporter (DAT) expression and dopamine reuptake. However, the time-course of diet-induced changes in DAT expression and function and whether such changes are dependent upon the development of DIO remains unresolved. Here, the authors fed rats a high (HFD) or low (LFD) fat diet for 2 or 6 weeks. Following diet exposure, rats were anesthetized with urethane and striatal DAT function was assessed by electrically stimulating the dopamine cell bodies in the ventral tegmental area (VTA) and recording resultant changes in dopamine concentration in the ventral striatum using fast-scan cyclic voltammetry. The authors also quantified the effect of HFD on membrane associated DAT in striatal cell fractions from a separate group of rats following exposure to the same diet protocol. Notably, none of our treatment groups differed in body weight. They found a deficit in the rate of dopamine reuptake in HFD rats relative to LFD rats after 6 but not 2 weeks of diet exposure. Additionally, the increase in evoked dopamine following a pharmacological challenge of cocaine was significantly attenuated in HFD relative to LFD rats. Western blot analysis revealed that there was no effect of diet on total DAT protein. However, 6 weeks of HFD exposure significantly reduced the 50 kDa DAT isoform in a synaptosomal membrane-associated fraction, but not in a fraction associated with recycling endosomes. These data provide further evidence for diet-induced alterations in dopamine reuptake independent of changes in DAT production and demonstrates that such changes can manifest without the development of DIO. Cone JJ, Chartoff EH, Potter DN, Ebner SR, Roitman MF. Prolonged high fat diet reduces dopamine reuptake without altering dat gene expression. PLoS One. 2013; 8(3):e58251. doi: 10.1371/journal.pone.0058251. Epub 2013 Mar 13.

Adolescent Morphine Exposure Affects Long-Term Microglial Function and Later-Life Relapse Liability In A Model Of Addiction Adolescence in humans represents a unique developmental time point associated with increased risk-taking behavior and experimentation with drugs of abuse. The authors hypothesized that exposure to drugs of abuse during adolescence may increase the risk of addiction in adulthood. To test this, rats were treated with a subchronic regimen of morphine or saline in adolescence, and their preference for morphine was examined using conditioned place preference (CPP) and drug-induced reinstatement in adulthood. The initial preference for morphine did not differ between groups; however, rats treated with morphine during adolescence showed robust reinstatement of morphine CPP after drug re-exposure in adulthood. This effect was not seen in rats pretreated with a subchronic regimen of morphine as adults, suggesting that exposure to morphine specifically during adolescence increases the risk of relapse to drug-seeking behavior in adulthood. The authors have previously established a role for microglia, the immune cells of the brain, and immune molecules in the risk of drug-induced reinstatement of morphine CPP. Thus, they examined the role of microglia within the nucleus accumbens of these rats and determined that rats exposed to morphine during adolescence had a significant increase in Toll-like receptor 4 (TLR4) mRNA and protein expression specifically on microglia. Morphine binds to TLR4 directly, and this increase in TLR4 was associated with exaggerated morphine-induced TLR4 signaling and microglial activation in rats previously exposed to morphine during adolescence. These data suggest that long-term changes in microglial function, caused by adolescent morphine exposure, alter the risk of drug-induced reinstatement in adulthood. Schwarz JM, Bilbo SD. Adolescent morphine exposure affects long-term microglial function and later-life relapse liability in a model of addiction. J Neurosci 2013; 33(3): 961-971.

Inhalation Exposure To Smoke From Synthetic 'Marijuana' Produces Potent Cannabimimetic Effects In Mice Use of synthetic "marijuana" has increased in recent years, produced adverse effects and prompted the temporary DEA ban of five specific cannabinoid analogs, including JWH-018. The objectives of the current study include determining the chemical content of the herbal product, Buzz, assessing its behavioral effects upon inhalation exposure to mice, determining whether CB(1) receptors mediate its pharmacological activity, and ascertaining its biodisposition in blood and various organs. Using a nose-only exposure system, mice were exposed to smoke produced from combustion of an herbal incense product, Buzz, which contained 5.4% JWH-018. Cannabimimetic effects following smoke exposure were evaluated using the tetrad procedure, consisting of the following indices: hypomotility, antinociception, catalepsy, and hypothermia. Additionally, blood and tissues were collected for JWH-018 quantification. Inhalation exposure to Buzz produced dose-related tetrad effects similar to marijuana as well as dose-related increased levels of JWH-018 in the blood, brain, heart, kidney, liver, lung, and spleen. The behavioral effects were blocked by rimonabant, a CB(1) receptor antagonist. Effects produced by Buzz were similar in magnitude and time-course to those produced by marijuana, though equipotent doses of Buzz and marijuana yielded considerably lower brain levels of JWH-018 than THC for the respective materials. The authors conclude that inhalation exposure to a product containing JWH-018 penetrates into the brain and other organs and produces CB(1) receptor-mediated behavioral pharmacological effects in mice. The increased potency of JWH-018 compared to THC, the variable amount of drug added to various herbal products, and unknown toxicity, undoubtedly contribute to public health risks of synthetic cannabinoids. Wiebelhaus JM, Poklis JL, Poklis A, Vann RE, Lichtman AH, Wise LE. Inhalation exposure to smoke from synthetic 'marijuana' produces potent cannabimimetic effects in mice. Drug Alcohol Depend 2012;: 126(3): 316-323.

Effects Upon In-Vivo Nicotine Metabolism Reveal Functional Variation In FMO3 Associated With Cigarette Consumption Flavin-containing monooxygenases (FMO) catalyze the metabolism of nucleophilic heteroatom-containing drugs and xenobiotics, including nicotine. Rare mutations in FMO3 are responsible for defective N-oxidation of dietary trimethylamine leading to trimethylaminuria, and common genetic variation in FMO3 has been linked to interindividual variability in metabolic function that may be substrate specific. A genetic model of CYP2A6 function is used as a covariate to reveal functional polymorphism in FMO3 that indirectly influences the ratio of deuterated nicotine metabolized to cotinine following oral administration. The association is tested between FMO3 haplotype and cigarette consumption in a set of nicotine-dependent smokers. FMO3 haplotype, based on all common coding variants in Europeans, significantly predicts nicotine metabolism and accounts for ~2% of variance in the apparent percent of nicotine metabolized to cotinine. The metabolic ratio is not associated with FMO2 haplotype or an FMO1 expression quantitative trait locus. Cross-validation demonstrates calculated FMO3 haplotype parameters to be robust and significantly improve the predictive nicotine metabolism model over CYP2A6 genotype alone. Functional classes of FMO3 haplotypes, as determined by their influence on nicotine metabolism to cotinine, are also significantly associated with cigarettes per day in nicotine-dependent European Americans (n=1025, P=0.04), and significantly interact (P=0.016) with CYP2A6 genotype to predict cigarettes per day. These findings suggest that common polymorphisms in FMO3 influence nicotine clearance and that these genetic variants in turn influence cigarette consumption. Bloom AJ, Murphy SE, Martinez M, von Weymarn LB, Bierut LJ, Goate A. Effects upon in-vivo nicotine metabolism reveal functional variation in FMO3 associated with cigarette consumption. Pharmacogenet Genomics 2013; 23(2): 62-68.

HDAC3-Selective Inhibitor Enhances Extinction Of Cocaine-Seeking Behavior In A Persistent Manner Nonspecific histone deacetylase (HDAC) inhibition has been shown to facilitate the extinction of drug-seeking behavior in a manner resistant to reinstatement. A key open question is which specific HDAC is involved in the extinction of drug-seeking behavior. Using the selective HDAC3 inhibitor RGFP966, the authors investigated the role of HDAC3 in extinction and found that systemic treatment with RGFP966 facilitates extinction in mice in a manner resistant to reinstatement. They also investigated whether the facilitated extinction is related to the enhancement of extinction consolidation during extinction learning or to negative effects on performance or reconsolidation. These are key distinctions with regard to any compound being used to modulate extinction, because a more rapid decrease in a defined behavior is interpreted as facilitated extinction. Using an innovative combination of behavioral paradigms, the authors found that a single treatment of RGFP966 enhances extinction of a previously established cocaine-conditioned place preference, while simultaneously enhancing long-term object-location memory within subjects. During extinction consolidation, HDAC3 inhibition promotes a distinct pattern of histone acetylation linked to gene expression within the infralimbic cortex, hippocampus, and nucleus accumbens. Thus, the facilitated extinction of drug-seeking cannot be explained by adverse effects on performance. These results demonstrate that HDAC3 inhibition enhances the memory processes involved in extinction of drug-seeking behavior. Malvaez M, McQuown SC, Rogge GA, Astarabadi M, Jacques V, Carreiro S, Rusche JR, Wood MA. HDAC3-selective inhibitor enhances extinction of cocaine-seeking behavior in a persistent manner. Proc Natl Acad Sci U S A. 2013 Feb 12; 110(7): 2647-2652. doi: 10.1073/pnas.1213364110. Epub 2013 Jan 7.

Social Deprivation Enhances VTA Synaptic Plasticity and Drug-Induced Contextual Learning Drug addiction is driven, in part, by powerful drug-related memories. Deficits in social life, particularly during adolescence, increase addiction vulnerability. Social isolation in rodents has been used extensively to model the effects of deficient social experience, yet its impact on learning and memory processes underlying addiction remains elusive. Here, the authors show that social isolation of rats during a critical period of adolescence (postnatal days 21-42) enhances long-term potentiation of NMDA receptor (NMDAR)-mediated glutamatergic transmission in the ventral tegmental area (VTA). This enhancement, which is caused by an increase in metabotropic glutamate receptor-dependent Ca(2+) signaling, cannot be reversed by subsequent resocialization. Notably, memories of amphetamine- and ethanol-paired contextual stimuli are acquired faster and, once acquired, amphetamine-associated contextual memory is more resistant to extinction in socially isolated rats. The authors propose that NMDAR plasticity in the VTA may represent a neural substrate by which early life deficits in social experience increase addiction vulnerability. Whitaker LR, Degoulet M, Morikawa H. Social Deprivation Enhances VTA Synaptic Plasticity and Drug-Induced Contextual Learning. Neuron 2013; 77(2): 335-345.

Clinically Employed Opioid Analgesics Produce Antinociception via μ-δ Opioid Receptor Heteromers in Rhesus Monkeys Morphine and related drugs are widely employed as analgesics despite the side effects associated with their use. Although morphine is thought to mediate analgesia through mu opioid receptors, delta opioid receptors have been implicated in mediating some side effects such as tolerance and dependence. Here the authors present evidence in rhesus monkeys that morphine, fentanyl, and possibly methadone selectively activate mu-delta heteromers to produce antinociception that is potently antagonized by the delta opioid receptor antagonist, naltrindole (NTI). Studies with HEK293 cells expressing mu-delta heteromeric opioid receptors exhibit a similar antagonism profile of receptor activation in the presence of NTI. In mice, morphine was potently inhibited by naltrindole when administered intrathecally, but not intracerebroventricularly, suggesting the possible involvement of mu-delta heteromers in the spinal cord of rodents. Taken together, these results strongly suggest that, in primates, mu-delta heteromers are allosterically coupled and mediate the antinociceptive effects of three clinically employed opioid analgesics that have been traditionally viewed as mu-selective. Given the known involvement of delta receptors in morphine tolerance and dependence, the present results implicate mu-delta heteromers in mediating both antinociception and these side effects in primates. These results open the door for further investigation in humans., Yekkirala AS, Banks ML, Lunzer MM, Negus SS, Rice KC, Portoghese PS. ACS Chem Neurosci. 2012 Sep 19; 3(9): 720-727. Epub 2012 Jul 5.

Rat Ultrasonic Vocalizations Demonstrate that the Motivation To Contextually Reinstate Cocaine-Seeking Behavior Does Not Necessarily Involve A Hedonic Response Human self-reports often indicate that changes in mood are a major contributor to drug relapse. Still, arguments have been made that instances of drug-seeking following abstinence in animal models (i.e. relapse/reinstatement) may be outside of hedonic control. Therefore, the present study utilized ultrasonic vocalizations in the rat in order to evaluate affect during cocaine self-administration and contextual reinstatement of cocaine-seeking in a pre-clinical model of drug relapse (abstinence-reinstatement model). Results show that while subjects effectively reinstated drug-seeking (lever pressing) following 30 days of abstinence, and spontaneously recovered/reinstated drug-seeking following 60 days of abstinence, ultrasonic vocalizations did not increase over baseline levels during either reinstatement session. These results are consistent with previous results from the authors' laboratory and current theories of addiction suggesting that cues that are weakly associated with drug consumption can motivate drug-seeking behavior that is outside of hedonic processing.

Barker DJ, Bercovicz D, Servilio LC, Simmons SJ, Ma S, Root DH, Pawlak AP, West MO. Rat ultrasonic vocalizations demonstrate that the motivation to contextually reinstate cocaine-seeking behavior does not necessarily involve a hedonic response. Addict Biol. 2013 Mar 18. doi: 10.1111/adb.12044. [Epub ahead of print].

Behavioral and Structural Responses to Chronic Cocaine Require a Feedforward Loop Involving ΔFosB and Calcium/Calmodulin-Dependent Protein Kinase II in the Nucleus Accumbens Shell The transcription factor ΔFosB and the brain-enriched calcium/calmodulin-dependent protein kinase II (CaMKIIα) are induced in the nucleus accumbens (NAc) by chronic exposure to cocaine or other psychostimulant drugs of abuse, in which the two proteins mediate sensitized drug responses. Although ΔFosB and CaMKIIα both regulate AMPA glutamate receptor expression and function in NAc, dendritic spine formation on NAc medium spiny neurons (MSNs), and locomotor sensitization to cocaine, no direct link between these molecules has to date been explored. Here, the authors demonstrate that ΔFosB is phosphorylated by CaMKIIα at the protein-stabilizing Ser27 and that CaMKII is required for the cocaine-mediated accumulation of ΔFosB in rat NAc. Conversely, they show that ΔFosB is both necessary and sufficient for cocaine induction of CaMKIIα gene expression in vivo, an effect selective for D_1-type MSNs in the NAc shell subregion. Furthermore, induction of dendritic spines on NAc MSNs and increased behavioral responsiveness to cocaine after NAc overexpression of ΔFosB are both CaMKII dependent. Importantly, the authors demonstrate for the first time induction of ΔFosB and CaMKII in the NAc of human cocaine addicts, suggesting possible targets for future therapeutic intervention. These data establish that ΔFosB and CaMKII engage in a cell-type- and brain-region-specific positive feedforward loop as a key mechanism for regulating the reward circuitry of the brain in response to chronic cocaine. Robison AJ, Vialou V, Mazei-Robison M, Feng J, Kourrich S, Collins M, Wee S, Koob G, Turecki G, Neve R, Thomas M, Nestler EJ. Behavioral and structural responses to chronic cocaine require a feedforward loop involving δfosb and calcium/calmodulin-dependent protein kinase ii in the nucleus accumbens shell. J Neurosci. 2013 Mar 6; 33(10): 4295-4307.

Dose-Related Effects Of Salvinorin A In Humans: Dissociative, Hallucinogenic, and Memory Effects Salvinorin A is a kappa opioid agonist and the principal psychoactive constituent of the plant Salvia divinorum, which has increased in popularity as a recreational drug over the past decade. Few human studies have examined salvinorin A. This double-blind, placebo-controlled study evaluated the dose-related effects of inhaled salvinorin A in individuals with histories of hallucinogen use. Eight healthy hallucinogen-using adults inhaled up to 16 doses of salvinorin A (0.375-21 μg/kg) in ascending order. Physiological, behavioral, and subjective effects were assessed every 2 min for 60 min after administration. Qualitative subjective effects were assessed retrospectively via questionnaires at the end of sessions. Persisting effects were assessed 1 month later. Orderly dose-related effects peaked at 2 min and then rapidly dissipated, replicating previous findings. Subjective effects were intense, with maximal drug strength ratings or unresponsiveness frequently observed at high doses. Questionnaires assessing qualitative effects (Hallucinogen Rating Scale, Pharmacological Class Questionnaire) suggested some overlap with serotonergically mediated classic hallucinogens. Salvinorin A also produced dose-related dissociative effects and impairments in recall/recognition memory. At 1-month follow-up, there was no evidence of persisting adverse effects. Participants reported that salvinorin A effects were qualitatively different from other drugs. Salvinorin A produces a unique profile of subjective and cognitive effects, including strong dissociative effects and memory impairment, which only partially overlap with classic hallucinogen effects. Along with nonhuman studies of salvinorin A, these results are important for understanding the neurobiology of the kappa opioid system and may ultimately have

important therapeutic applications. Maclean KA, Johnson MW, Reissig CJ, Prisinzano TE, Griffiths RR. Dose-related effects of salvinorin A in humans: dissociative, hallucinogenic, and memory effects. Psychopharmacology (Berl) 2013; 226(2): 381-392.

Instant Transformation Of Learned Repulsion Into Motivational 'Wanting' Learned cues for pleasant reward often elicit desire, which, in addicts, may become compulsive. According to the dominant view in addiction neuroscience and reinforcement modeling, such desires are the simple products of learning, coming from a past association with reward outcome. The authors demonstrate that cravings are more than merely the products of accumulated pleasure memories-even a repulsive learned cue for unpleasantness can become suddenly desired via the activation of mesocorticolimbic circuitry. Rats learned repulsion toward a Pavlovian cue (a briefly-inserted metal lever) that always predicted an unpleasant Dead Sea saltiness sensation. Yet, upon first reencounter in a novel sodium-depletion state to promote mesocorticolimbic reactivity (reflected by elevated Fos activation in ventral tegmentum, nucleus accumbens, ventral pallidum, and the orbitofrontal prefrontal cortex), the learned cue was instantly transformed into an attractive and powerful motivational magnet. Rats jumped and gnawed on the suddenly attractive Pavlovian lever cue, despite never having tasted intense saltiness as anything other than disgusting. Instant desire transformation of a learned cue contradicts views that Pavlovian desires are essentially based on previously learned values (e.g., prediction error or temporal difference models). Instead desire is recomputed at reencounter by integrating Pavlovian information with the current brain/physiological state. This powerful brain transformation reverses strong learned revulsion into avid attraction. When applied to addiction, related mesocorticolimbic transformations (e.g., drugs or neural sensitization) of cues for already-pleasant drug experiences could create even more intense cravings. This cue/state transformation helps define what it means to say that addiction hijacks brain limbic circuits of natural reward. Robinson MJF, Berridge KC. Instant transformation of learned repulsion into motivational 'wanting'. Curr Biol 2013; 23(4): 282-289.

The Neuron-Specific Chromatin Regulatory Subunit BAF53b Is Necessary For Synaptic Plasticity and Memory Recent exome sequencing studies have implicated polymorphic Brg1-Associated Factor (BAF) complexes (mammalian SWI/SNF chromatin remodeling complexes) in several human intellectual disabilities and cognitive disorders. However, it is currently unknown how mutations in BAF complexes result in impaired cognitive function. Postmitotic neurons express a neuron-specific assembly, nBAF, characterized by the neuron-specific subunit BAF53b. Mice harboring selective genetic manipulations of BAF53b have severe defects in long-term memory and long-lasting forms of hippocampal synaptic plasticity. The authors rescued memory impairments in BAF53b mutant mice by reintroducing BAF53b in the adult hippocampus, which suggests a role for BAF53b beyond neuronal development. The defects in BAF53b mutant mice appeared to derive from alterations in gene expression that produce abnormal postsynaptic components, such as spine structure and function, and ultimately lead to deficits in synaptic plasticity. These results provide new insight into the role of dominant mutations in subunits of BAF complexes in human intellectual and cognitive disorders. Vogel-Ciernia A, Matheos DP, Barrett RM, Kramár EA, Azzawi S, Chen Y, Magnan CN, Zeller M, Sylvain A, Haettig J, Jia Y, Tran A, Dang R, Post RJ, Chabrier M, Babayan AH, Wu JI, Crabtree GR, Baldi P, Baram TZ, Lynch G, Wood MA. The neuron-specific chromatin regulatory subunit BAF53b is necessary for synaptic plasticity and memory. Nat Neurosci. 2013 Mar 24. [Epub ahead of print].

Hierarchical Recruitment Of Phasic Dopamine Signaling In the Striatum During the Progression Of Cocaine Use Drug addiction is a neuropsychiatric disorder that marks the end stage of a progression beginning with recreational drug taking but culminating in habitual and compulsive drug use. This progression is considered to reflect transitions among multiple neural loci. Dopamine neurotransmission in the ventromedial striatum (VMS) is pivotal in the control of initial drug use, but emerging evidence indicates that once drug use is well established, its control is dominated by the dorsolateral striatum (DLS). In the current work, the authors conducted longitudinal neurochemical recordings to ascertain the spatiotemporal profile of striatal dopamine release and to investigate how it changes during the period from initial to established drug use. Dopamine release was detected using fast-scan cyclic voltammetry simultaneously in the VMS and DLS of rats bearing indwelling i.v. catheters over the course of 3 wk of cocaine self-administration. The authors found that phasic dopamine release in DLS emerged progressively during drug taking over the course of weeks, a period during which VMS dopamine signaling declined. This emergent dopamine signaling in the DLS mediated discriminated behavior to obtain drug but did not promote escalated or compulsive drug use. The authors also demonstrate that this recruitment of dopamine signaling in the DLS is dependent on antecedent activity in VMS circuitry. Thus, the current findings identify a striatal hierarchy that is instantiated during the expression of established responses to obtain cocaine. Willuhn I, Burgeno LM, Everitt BJ, Phillips PEM. Hierarchical recruitment of phasic dopamine signaling in the striatum during the progression of cocaine use. Proc Natl Acad Sci U S A 2012; 109(50): 20703-10708.

Novel Insights Into CB1 Cannabinoid Receptor Signaling: A Key Interaction Identified Between EC3-Loop and TMH2 Activation of the CB1 receptor is modulated by aspartate residue D2.63(176) in transmembrane helix (TMH) II. Interestingly, D2.63 does not affect the affinity for ligand binding at the CB1 receptor. Studies in class A GPCRs have suggested an ionic interaction between residues of TMHII and VII. In this report, modeling studies identified residue K373, in the extracellular (EC)-3 loop, in charged interactions with D2.63. We investigated this possibility by performing reciprocal mutations and biochemical studies. D2.63A, K373A, D2.63A-K373A, and the reciprocal mutant with the interacting residues juxtaposed, D2.63K-K373D, were characterized using radioligand binding and guanosine 5'-3-O-(thio)triphosphate (GTPγS) functional assays. None of the mutations resulted in a significant change in the binding affinity of N-(piperidiny-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride (SR141716A) or (-)-3cis -[2-hydroxyl-4-(1,1-dimethyl-heptyl)phenyl]-trans-4-[3-hydroxyl-propyl] cyclohexan-1-ol (CP55,940). Modeling studies indicated that binding site interactions and energies of interaction for CP55,940 were similar between WT and mutant receptors. However, the signaling of CP55,940, and (R)-(+)-[2,3-dihydro-5-methyl-3-[(4-morpholinyl)methyl]-pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl](1-naphthalenyl)-methanone mesylate (WIN55,212-2) was impaired at the D2.63A-K373A and the single alanine mutants. In contrast, the reciprocal D2.63K-K373D mutant regained function for both CP55,940 and WIN55,212-2. Computational results indicate that the D2.63-K373 ionic interaction strongly influences the conformation(s) of the EC-3 loop, providing a structure-based rationale for the importance of the EC-3 loop to signal transduction in CB1. The putative ionic interaction results in the EC-3 loop pulling over the top (extracellular side) of the receptor; this EC-3 loop conformation may serve protective and mechanistic roles. These results suggest that the ionic interaction between D2.63 and K373 is important for CB1 signal transduction. Marcu J, Shore DM, Kapur A, Trznadel M, Makriyannis A, Reggio PH, Abood ME. Novel Insights into CB1 cannabinoid receptor signaling: A key interaction identified between ec3-loop and TMH2. J Pharmacol Exp Ther 2013. Epub ahead of print.

Adolescents Are More Vulnerable To Cocaine Addiction: Behavioral and Electrophysiological Evidence In humans, adolescence is a period of heightened propensity to develop cocaine addiction. It is unknown whether this is attributable to greater access and exposure to cocaine at this age, or whether the adolescent brain is particularly vulnerable to the addictive properties of cocaine. Here, the authors subjected male adolescent (P42) and adult (~P88) rats to a wide range of cocaine self-administration procedures. In addition, to determine whether behavioral differences are associated with developmental differences in dopaminergic activity, they examined and manipulated the activity of dopamine neurons. Relative to adults, adolescent rats took cocaine more readily, were more sensitive to lower doses, showed greater escalation of cocaine intake, and were less susceptible to increases in price (i.e., were more "inelastic"). In parallel, adolescents also showed elevated activity of ventral tegmental area dopamine neurons, a feature known to be associated with increased self-administration behavior. Pharmacological manipulation of dopamine D2 receptor function with quinpirole (agonist) or eticlopride (antagonist), to alter dopamine neuron activity, eliminated age differences in cocaine self-administration. These data suggest a causal relationship between behavioral and electrophysiological determinants of cocaine addiction liability. In conclusion, adolescents show behavioral and electrophysiological traits of heightened addiction liability. Wong WC, Ford KA, Pagels NE, McCutcheon JE, Marinelli M. Adolescents are more vulnerable to cocaine addiction: behavioral and electrophysiological evidence. J Neurosci. 2013 Mar 13; 33(11): 4913-4922.

Reduced Striatal Dopamine D1-D2 Receptor Heteromer Expression and Behavioural Subsensitivity In Juvenile Rats In adult rat striatum the dopamine D1-D2 receptor heteromer is expressed selectively in a subset of medium spiny neurons (MSNs) that coexpress the dopamine D1 and D2 receptors (D1R and D2R) as well as dynorphin (DYN) and enkephalin (ENK), with higher coexpression in nucleus accumbens (NAc) and much lower in the caudate putamen (CP). In the present study the authors showed that in neonatal striatal cultured neurons >90% exhibited the D1R/D2R-DYN/ENK phenotype. Similarly, in the striatum of juvenile rats (age 26-28 days) coexpression of D1R and D2R was also coincident with the expression of both DYN and ENK. Quantification of the number of striatal MSNs exhibiting coexpression of D1R and D2R in juvenile rats revealed significantly lower coexpression in NAc shell, but not core, and CP than in adult rats. However, within MSNs that coexpressed D1R and D2R, the propensity to form the D1-D2 receptor heteromer did not differ between age groups. Consistent with reduced coexpression of the D1R and D2R, juvenile rats exhibited subsensitivity to D1-D2 receptor heteromer-induced grooming following activation by SKF 83959. Given the proposed role of D1R/D2R-coexpressing MSNs in the regulation of thalamic output, and the recent discovery that these MSNs exhibit both inhibitory and excitatory capabilities, these findings suggest that the functional regulation of neurotransmission by the dopamine D1-D2 receptor heteromer within the juvenile striatum may be significantly different than in the adult. Perreault ML, Hasbi A, Alijaniaram M, O'Dowd BF, George SR. Reduced striatal dopamine D1-D2 receptor heteromer expression and behavioural subsensitivity in juvenile rats. Neuroscience 2012; 225: 130-139.

Mephedrone and Methylenedioxypyrovalerone (MDPV), Major Constituents Of 'Bath Salts,' Produce Opposite Effects At the Human Dopamine Transporter Psychoactive "bath salts" represent a relatively new drug of abuse combination that was placed in Schedule I in October 2011. Two common ingredients of bath salts include the cathinone analogs: mephedrone and methylenedioxypyrovalerone (MDPV). The mechanism of action of these synthetic cathinone analogs has not been well investigated. Because cathinone and methcathinone are known to act as releasing agents at the human dopamine transporter (hDAT), mephedrone and MDPV were

investigated at hDAT expressed in Xenopus oocytes. Whereas mephedrone was found to have the signature of a dopamine-releasing agent similar to methamphetamine or methcathinone, MDPV behaved as a cocaine-like reuptake inhibitor of dopamine. The authors conclude that mephedrone and MDPV produce opposite electrophysiological signatures through hDAT expressed in oocytes. Implications are that the combination (as found in bath salts) might produce effects similar to a combination of methamphetamine and cocaine. Cameron K, Kolanos R, Verkariya R, De Felice L, Glennon RA. Mephedrone and methylenedioxypyrovalerone (MDPV), major constituents of 'bath salts,' produce opposite effects at the human dopamine transporter. Psychopharmacology (Berl) 2013. Epub ahead of print.

Glucuronic Acid and the Ethanol Metabolite Ethyl-Glucuronide Cause Toll-Like Receptor 4 Activation and Enhanced Pain The authors have previously observed that the non-opioid morphine metabolite, morphine-3-glucuronide, enhances pain via a toll-like receptor 4 (TLR4) dependent mechanism. The present studies were undertaken to determine whether TLR4-dependent pain enhancement generalizes to other classes of glucuronide metabolites. In silico modeling predicted that glucuronic acid alone and ethyl glucuronide, a minor but long-lasting ethanol metabolite, would dock to the same MD-2 portion of the TLR4 receptor complex previously characterized as the docking site for morphine-3-glucuronide. Glucuronic acid, ethyl glucuronide and ethanol all caused an increase in TLR4-dependent reporter protein expression in a cell line transfected with TLR4 and associated co-signaling molecules. Glucuronic acid-, ethyl glucuronide-, and ethanol-induced increases in TLR4 signaling were blocked by the TLR4 antagonists LPS-RS and (+)-naloxone. Glucuronic acid and ethyl glucuronide both caused allodynia following intrathecal injection in rats, which was blocked by intrathecal co-administration of the TLR4 antagonist LPS-RS. The finding that ethyl glucuronide can cause TLR4-dependent pain could have implications for human conditions such as hangover headache and alcohol withdrawal hyperalgesia, as well as suggesting that other classes of glucuronide metabolites could have similar effects. Lewis SS, Hutchinson MR, Zhang Y, Hund DK, Maier SF, Rice KC, Watkins LR. Glucuronic acid and the ethanol metabolite ethyl-glucuronide cause toll-like receptor 4 activation and enhanced pain. Brain Behav Immun 2013. Epub ahead of print.

A Large-Scale Meta-Analysis of the Association Between The ANKK1/DRD2 Taq1A Polymorphism and Alcohol Dependence Alcohol dependence (AD) is a common neuropsychiatric disorder with high heritability. A number of studies have analyzed the association between the Taq1A polymorphism (located in the gene cluster ANKK1/DRD2) and AD. In the present study, the authors conducted a large-scale meta-analysis to confirm the association between the Taq1A polymorphism and the risk for AD in over 18,000 subjects included in 61 case-control studies that were published up to August 2012. The authors' meta-analysis demonstrated both allelic and genotypic association between the Taq1A polymorphism and AD susceptibility [allelic: $P(Z) = 1.1 \times 10(-5)$, OR = 1.19; genotypic: $P(Z) = 3.2 \times 10(-5)$, OR = 1.24]. The association remained significant after adjustment for publication bias using the trim and fill method. Sensitivity analysis showed that the effect size of the Taq1A polymorphism on AD risk was moderate and not influenced by any individual study. The pooled odds ratio from published studies decreased with the year of publication, but stabilized after the year 2001. Subgroup analysis indicated that publication bias could be influenced by racial ancestry. In summary, this large-scale meta-analysis confirmed the association between the Taq1A polymorphism and AD. Future studies are required to investigate the functional significance of the ANKK1/DRD2 Taq1A polymorphism in AD. Wang F, Simen A, Arias A, Lu QW, Zhang H. A large-scale meta-analysis of the association between the

ANKK1/DRD2 Taq1A polymorphism and alcohol dependence. Hum Genet 2012. Epub ahead of print.

The Synaptic Adhesion Molecule SynCAM 1 Contributes to Cocaine Effects on Synapse Structure and Psychostimulant Behavior Drugs of abuse have acute and persistent effects on synapse structure and addiction-related behaviors. Trans-synaptic interactions can control synapse development, and synaptic cell adhesion molecule (SynCAM) proteins (also named nectin-like molecules) are immunoglobulin adhesion proteins that span the synaptic cleft and induce excitatory synapses. The present studies now reveal that the loss of SynCAM 1 in knockout (KO) mice reduces excitatory synapse number in nucleus accumbens (NAc). SynCAM 1 additionally contributes to the structural remodeling of NAc synapses in response to the psychostimulant cocaine. Specifically, the authors find that cocaine administration increases the density of stubby spines on medium spiny neurons in NAc, and that maintaining this increase requires SynCAM 1. Furthermore, mushroom-type spines on these neurons are structurally more plastic when SynCAM 1 is absent, and challenging drug-withdrawn mice with cocaine shortens these spines in SynCAM 1 KO mice. These effects are correlated with changes on the behavioral level, where SynCAM 1 contributes to the psychostimulant effects of cocaine as measured after acute and repeated administration, and in drug-withdrawn mice. Together, these results provide evidence that the loss of a synapse-organizing adhesion molecule can modulate cocaine effects on spine structures in NAc and increases vulnerability to the behavioral actions of cocaine. SynCAM-dependent pathways may therefore represent novel points of therapeutic intervention after exposure to drugs of abuse. Giza JI, Jung Y, Jeffrey RA, Neugebauer NM, Picciotto MR, Biederer T. The synaptic adhesion molecule SynCAM 1 contributes to cocaine effects on synapse structure and psychostimulant behavior. Neuropsychopharmacology 2013; 38(4): 628-638.

Variation of the Net Charge, Lipophilicity, and Side Chain Flexibility in Dmt(1)-DALDA: Effect on Opioid Activity and Biodistribution The influence of the side chain charges of the second and fourth amino acid residues in the peptidic μ opioid lead agonist Dmt-d-Arg-Phe-Lys-NH(2) ([Dmt(1)]-DALDA) was examined. Additionally, to increase the overall lipophilicity of [Dmt(1)]-DALDA and to investigate the Phe(3) side chain flexibility, the final amide bond was N-methylated and Phe(3) was replaced by a constrained aminobenzazepine analogue. The in vitro receptor binding and activity of the peptides, as well as their in vivo transport (brain in- and efflux and tissue biodistribution) and antinociceptive properties after peripheral administration (ip and sc) in mice were determined. The structural modifications result in significant shifts of receptor binding, activity, and transport properties. Strikingly, while [Dmt(1)]-DALDA and its N-methyl analogue, Dmt-d-Arg-Phe-NMeLys-NH(2), showed a long-lasting antinociceptive effect (>7 h), the peptides with d-Cit(2) generate potent antinociception more rapidly (maximal effect at 1h postinjection) but also lose their analgesic activity faster when compared to [Dmt(1)]-DALDA and [Dmt(1),NMeLys(4)]-DALDA., Novoa A, Van Dorpe S, Wynendaele E, Spetea M, Bracke N, Stalmans S, Betti C, Chung NN, Lemieux C, Zuegg J, Cooper MA, Tourwé D, De Spiegeleer B, Schiller PW, Ballet S. J Med Chem 2012 Nov 26; 55(22): 9549-9561. doi: 10.1021/jm3008079. Epub 2012 Nov 12.

DAGLβ Inhibition Perturbs A Lipid Network Involved In Macrophage Inflammatory Responses The endocannabinoid 2-arachidonoylglycerol (2-AG) is biosynthesized by diacylglycerol lipases DAGLα and DAGLβ. Chemical probes to perturb DAGLs are needed to characterize endocannabinoid function in biological processes. Here we report a series of 1,2,3-triazole urea inhibitors, along with paired negative-control and activity-based probes, for the

functional analysis of DAGLβ in living systems. Optimized inhibitors showed high selectivity for DAGLβ over other serine hydrolases, including DAGLα (~60-fold selectivity), and the limited off-targets, such as ABHD6, were also inhibited by the negative-control probe. Using these agents and Daglb(-/-) mice, the authors show that DAGLβ inactivation lowers 2-AG, as well as arachidonic acid and eicosanoids, in mouse peritoneal macrophages in a manner that is distinct and complementary to disruption of cytosolic phospholipase-A2. They observed a corresponding reduction in lipopolysaccharide-induced tumor necrosis factor-α release. These findings indicate that DAGLβ is a key metabolic hub within a lipid network that regulates proinflammatory responses in macrophages. Hsu KL, Tsuboi K, Adibekian A, Pugh H, Masuda K, Cravatt BF. DAGLβ inhibition perturbs a lipid network involved in macrophage inflammatory responses. Nat Chem Biol 2012; 8(12): 999-1007.

Dopamine Transporter DAT and Receptor DRD2 Variants Affect Risk Of Lethal Cocaine Abuse: A Gene-Gene-Environment Interaction Epistatic gene-gene interactions could contribute to the heritability of complex multigenic disorders, but few examples have been reported. Here, the authors focus on the role of aberrant dopaminergic signaling, involving the dopamine transporter DAT, a cocaine target, and the dopamine D2 receptor, which physically interacts with DAT. Splicing polymorphism rs2283265 of DRD2, encoding D2 receptors, were shown to confer risk of cocaine overdose/death (odds ratio ~3) in subjects and controls from the Miami Dade County Brain Bank.(1) Risk of cocaine-related death attributable to the minor allele of rs2283265 was significantly enhanced to OR=7.5 (P=0.0008) in homozygous carriers of the main 6-repeat allele of DAT rs3836790, a regulatory VNTR in intron8 lacking significant effect itself. In contrast, carriers of the minor 5-repeat DAT allele showed no significant risk (OR=1.1, P=0.84). DAT rs3836790 and DRD2 rs2283265 also interacted by modulating DAT protein activity in the ventral putamen of cocaine abusers. In high-linkage disequilibrium with the VNTR, DAT rs6347 in exon9 yielded similar results. Assessing the impact of DAT alone, a rare DAT haplotype formed by the minor alleles of rs3836790 and rs27072, a regulatory DAT variant in the 3'-UTR, occurred in nearly one-third of the cocaine abusers but was absent in African American controls, apparently conferring strong risk. These results demonstrate gene-gene-drug interaction affecting risk of fatal cocaine intoxication. Sullivan D, Pinsonneault JK, Papp AC, Zhu H, Lemeshow S, Mash DC, Sadee W. Dopamine transporter DAT and receptor DRD2 variants affect risk of lethal cocaine abuse: a gene-gene-environment interaction. Transl Psychiatry. 2013 Jan 22; 3: e222.

Crebinostat: A Novel Cognitive Enhancer That Inhibits Histone Deacetylase Activity and Modulates Chromatin-Mediated Neuroplasticity Long-term memory formation is known to be critically dependent upon de novo gene expression in the brain. As a consequence, pharmacological enhancement of the transcriptional processes mediating long-term memory formation provides a potential therapeutic strategy for cognitive disorders involving aberrant neuroplasticity. Here the authors focus on the identification and characterization of small molecule inhibitors of histone deacetylases (HDACs) as enhancers of CREB (cAMP response element-binding protein)-regulated transcription and modulators of chromatin-mediated neuroplasticity. Using a CREB reporter gene cell line, theye screened a library of small molecules structurally related to known HDAC inhibitors leading to the identification of a probe we termed crebinostat that produced robust activation of CREB-mediated transcription. Further characterization of crebinostat revealed its potent inhibition of the deacetylase activity of recombinant class I HDACs 1, 2, 3, and class IIb HDAC6, with weaker inhibition of the class I HDAC8 and no significant inhibition of the class IIa HDACs 4, 5, 7, and 9. In cultured mouse primary neurons, crebinostat potently induced acetylation of both histone H3 and histone H4 as well as enhanced the expression of the CREB target gene Egr1 (early growth

response 1). Using a hippocampus-dependent, contextual fear conditioning paradigm, mice systemically administered crebinostat for a ten day time period exhibited enhanced memory. To gain insight into the molecular mechanisms of memory enhancement by HDAC inhibitors, whole genome transcriptome profiling of cultured mouse primary neurons treated with crebinostat, combined with bioinformatic analyses of CREB-target genes, was performed revealing a highly connected protein-protein interaction network reflecting modules of genes important to synaptic structure and plasticity. Consistent with these findings, crebinostat treatment increased the density of synapsin-1 punctae along dendrites in cultured neurons. Finally, crebinostat treatment of cultured mouse primary neurons was found to upregulate Bdnf (brain-derived neurotrophic factor) and Grn (granulin) and downregulate Mapt (tau) gene expression-genes implicated in aging-related cognitive decline and cognitive disorders. Taken together, these results demonstrate that crebinostat provides a novel probe to modulate chromatin-mediated neuroplasticity and further suggests that pharmacological optimization of selective of HDAC inhibitors may provide an effective therapeutic approach for human cognitive disorders. This article is part of a Special Issue entitled 'Cognitive Enhancers'. Fass DM, Reis SA, Ghosh B, Hennig KM, Joseph NF, Zhao WN, Nieland TJF, Guan JS, Kuhnle CEG, Tang W, Barker DD, Mazitschek R, Schreiber SL, Tsai LH, Haggarty SJ. Crebinostat: a novel cognitive enhancer that inhibits histone deacetylase activity and modulates chromatin-mediated neuroplasticity. Neuropharmacology 2013; 64: 81-96.

MicroRNA-182 Regulates Amygdala-Dependent Memory Formation De novo protein synthesis supports long-lasting functional and structural plasticity and is a molecular requirement for new memory formation. Recent evidence has suggested that microRNAs may be involved in regulating the molecular mechanisms underlying neural plasticity. MicroRNAs are endogenous, noncoding RNAs capable of post-transcriptional repression of their mRNA targets. To explore the potential for microRNA-mediated regulation of amygdala-dependent memory formation, the authors performed expression profiling of microRNAs in the lateral amygdala of rats 1 h after auditory fear conditioning. Microarray analysis revealed that over half of all known microRNAs are endogenously expressed in the lateral amygdala, with 7 microRNAs upregulated and 32 downregulated by auditory fear training. Bioinformatic analysis identified several of the downregulated microRNAs as potential repressors of actin-regulating proteins known to be involved in plasticity and memory. Downregulation of one of these microRNAs by auditory fear conditioning, miR-182, was confirmed by quantitative real-time PCR. Overexpression of miR-182 within the lateral amygdala resulted in decreased expression of the protein but not mRNA of two synapse-enriched regulators of actin known to modulate structural plasticity, cortactin and Rac1. The overexpression of miR-182 also disrupted long-term but not short-term auditory fear memory. These data indicate that learning-induced suppression of miR-182, a microRNA previously uncharacterized in the brain, supports long-term memory formation in the amygdala and suggests it does so, at least in part, through the derepression of key actin-regulating proteins. These findings further indicate that microRNAs may represent a previously underappreciated mechanism for regulating protein synthesis during memory consolidation. Griggs EM, Young EJ, Rumbaugh G, Miller CA. MicroRNA-182 regulates amygdala-dependent memory formation. J Neurosci. 2013 Jan 23; 33(4): 1734-1740.

Altered Dendritic Distribution Of Dopamine D2 Receptors and Reduction In Mitochondrial Number In Parvalbumin-Containing Interneurons In the Medial Prefrontal Cortex Of Cannabinoid-1 (CB1) Receptor Knockout Mice The prelimbic prefrontal cortex (PL) is a brain region integral to complex behaviors that are highly influenced by cannabinoids and by dopamine D2 receptor (D2R)-mediated regulation of fast-firing parvalbumin-containing interneurons. The

authors have recently shown that constitutive deletion of the cannabinoid-1 receptor (CB1R) greatly reduces parvalbumin levels in these neurons. The effects of CB1R deletion on PL parvalbumin interneurons may be ascribed to loss of CB1R-mediated retrograde signaling on mesocortical dopamine transmission, and, in turn, altered expression and/or subcellular distribution of D2R in the PL. Furthermore, diminished parvalbumin expression could indicate metabolic changes in fast-firing interneurons that may be reflected in changes in mitochondrial density in this population. The authors therefore comparatively examined electron microscopic dual labeling of D2R and parvalbumin in CB1 (-/-) and CB1 (+/+) mice to test the hypothesis that absence of CB1R produces changes in D2R localization and mitochondrial distribution in parvalbumin-containing interneurons of the PL. CB1 (-/-) mice had a significantly lower density of cytoplasmic D2R-immunogold particles in medium parvalbumin-labeled dendrites and a concomitant increase in the density of these particles in small dendrites. These dendrites received both excitatory and inhibitory-type synapses from unlabeled terminals and contained many mitochondria, whose numbers were significantly reduced in CB1 (-/-) mice. Non-parvalbumin dendrites showed no between-group differences in either D2R distribution or mitochondrial number. These results suggest that cannabinoid signaling provides an important determinant of dendritic D2 receptor distribution and mitochondrial availability in fast-spiking interneurons. Fitzgerald ML, Chan J, Mackie K, Lupica CR, Pickel VM. Altered dendritic distribution of dopamine D2 receptors and reduction in mitochondrial number in parvalbumin-containing interneurons in the medial prefrontal cortex of cannabinoid-1 (CB1) receptor knockout mice. J Comp Neurol 2012; 520(17): 4013-4031.

Constitutive Knockout Of the Membrane Cytoskeleton Protein Beta Adducin Decreases Mushroom Spine Density In the Nucleus Accumbens But Does Not Prevent Spine Remodeling In Response To Cocaine The adducin family of proteins associates with the actin cytoskeleton in a calcium-dependent manner. Beta adducin (βAdd) is involved in synaptic plasticity in the hippocampus; however, the role of βAdd in synaptic plasticity in other brain areas is unknown. Using diolistic labeling with the lipophilic dye DiI, the authos found that the density of mature mushroom-shaped spines was significantly decreased in the nucleus accumbens (NAc) in brain slices from βAdd-knockout (KO) mice as compared to their wildtype (WT) siblings. The effect of 10 days of daily cocaine (15 mg/kg) administration on NAc spine number and locomotor behavior was also measured in βAdd WT and KO mice. As expected, there was a significant increase in overall spine density in NAc slices from cocaine-treated WT mice at this time-point; however, there was a greater increase in the density of mushroom spines in βAdd-KO animals following chronic cocaine administration than in WT. In addition, βAdd-KO mice showed elevated locomotor activity in response to cocaine treatment compared to WT siblings. These results indicate that βAdd is required for stabilising mature spines under basal conditions in the NAc, but that lack of this protein does not prevent synaptic remodeling following repeated cocaine administration. In addition, these data are consistent with previous studies suggesting that βAdd may normally be involved in stabilising spines once drug- or experience-dependent remodeling has occurred. Jung Y, Mulholland PJ, Wiseman SL, Judson Chandler L, Picciotto MR. Constitutive knockout of the membrane cytoskeleton protein beta adducin decreases mushroom spine density in the nucleus accumbens but does not prevent spine remodeling in response to cocaine. Eur J Neurosci 2013; 37(1): 1-9.

MicroRNA 339 Down-Regulates M-Opioid Receptor At the Post-Transcriptional Level In Response To Opioid Treatment μ-Opioid receptor (MOR) level is directly related to the function of opioid drugs, such as morphine and fentanyl. Although agonist treatment generally does not affect transcription of mor, previous studies suggest that morphine can affect the translation efficiency of MOR transcript via microRNAs (miRNAs). On the basis of miRNA microarray

analyses of the hippocampal total RNA isolated from mice chronically treated with μ-opioid agonists, the authors found a miRNA (miR-339-3p) that was consistently and specifically increased by morphine (2-fold) and by fentanyl (3.8-fold). miR-339-3p bound to the MOR 3'-UTR and specifically suppressed reporter activity. Suppression was blunted by adding miR-339-3p inhibitor or mutating the miR-339-3p target site. In cells endogenously expressing MOR, miR-339-3p inhibited the production of MOR protein by destabilizing MOR mRNA. Up-regulation of miR-339-3p by fentanyl (EC(50)=0.75 nM) resulted from an increase in primary miRNA transcript. Mapping of the miR-339-3p primary RNA and its promoter revealed that the primary miR-339-3p was embedded in a noncoding 3'-UTR region of an unknown host gene and was coregulated by the host promoter. The identified promoter was activated by opioid agonist treatment (10 nM fentanyl or 10 μM morphine), a specific effect blocked by the opioid antagonist naloxone (10 μM). Taken together, these results suggest that miR-339-3p may serve as a negative feedback modulator of MOR signals by regulating intracellular MOR biosynthesis. Wu Q, Hwang CK, Zheng H, Wagley Y, Lin HY, Kim do K, Law PY, Loh HH, Wei LN. MicroRNA 339 down-regulates μ-opioid receptor at the post-transcriptional level in response to opioid treatment. FASEB J. 2013 Feb; 27(2): 522-535. doi: 10.1096/fj.12-213439. Epub 2012 Oct 19.

A Binding Site For Nonsteroidal Anti-Inflammatory Drugs In Fatty Acid Amide Hydrolase
In addition to inhibiting the cyclooxygenase (COX)-mediated biosynthesis of prostanoids, various widely used nonsteroidal anti-inflammatory drugs (NSAIDs) enhance endocannabinoid signaling by blocking the anandamide-degrading membrane enzyme fatty acid amide hydrolase (FAAH). The X-ray structure of FAAH in complex with the NSAID carprofen, along with site-directed mutagenesis, enzyme activity assays, and NMR analysis, has revealed the molecular details of this interaction, providing information that may guide the design of dual FAAH-COX inhibitors with superior analgesic efficacy. Bertolacci L, Romeo E, Veronesi M, Magotti P, Albani C, Dionisi M, Lambruschini C, Scarpelli R, Cavalli A, De Vivo M, Piomelli D, Garau G. A binding site for nonsteroidal anti-inflammatory drugs in fatty acid amide hydrolase. J Am Chem Soc 2013; 135(1): 22-25.

Relapse Induced By Cues Predicting Cocaine Depends On Rapid, Transient Synaptic Potentiation Cocaine addiction is characterized by long-lasting vulnerability to relapse arising because neutral environmental stimuli become associated with drug use and then act as cues that induce relapse. It is not known how cues elicit cocaine seeking, and why cocaine seeking is more difficult to regulate than seeking a natural reward. The authors found that cocaine-associated cues initiate cocaine seeking by inducing a rapid, transient increase in dendritic spine size and synaptic strength in the nucleus accumbens. These changes required neural activity in the prefrontal cortex. This is not the case when identical cues were associated with obtaining sucrose, which did not elicit changes in spine size or synaptic strength. The marked cue-induced synaptic changes in the accumbens were correlated with the intensity of cocaine, but not sucrose seeking, and may explain the difficulty addicts experience in managing relapse to cocaine use. Gipson CD, Kupchik YM, Shen H, Reissner KJ, Thomas CA, Kalivas PW. Relapse induced by cues predicting cocaine depends on rapid, transient synaptic potentiation. Neuron 2013 Mar 6; 77(5): 867-872. doi: 10.1016/j.neuron. 2013.01.005.

Retrodialysis of N/OFQ Into The Nucleus Accumbens Shell Blocks Cocaine-Induced Increases In Extracellular Dopamine and Locomotor Activity Nociceptin (N/OFQ) has been implicated in a variety of neurological disorders, most notably in reward processes and drug abuse. N/OFQ suppresses extracellular dopamine in the nucleus accumbens (NAc) after intracerebroventricular

injection. This study sought to examine the effects of retrodialyzed N/OFQ on the cocaine-induced increase in extracellular dopamine levels in the NAc, as well as locomotor activity, in freely moving rats. 1.0μM, 10μM, and 1mM N/OFQ, in the NAc shell, significantly suppressed the cocaine-induced dopamine increase in the NAc, while N/OFQ alone had no significant effect on dopamine levels. Co-delivery of the selective NOP receptor antagonist SB612111 ([(-)-cis-1-Methyl-7-[[4-(2,6-dichlorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol] reversed the N/OFQ suppression of cocaine-induced dopamine in the NAc, suggesting that this is an NOP receptor-mediated effect. Using a novel system to assess locomotion, the authors measured various motor activities of the animals with simultaneous microdialysis from the home cage. Cocaine produced an expected increase in total activity, including horizontal movement and rearing behavior. Retrodialysis of N/OFQ with cocaine administration affected all motor activities, initially showing no effect on behavior, but over time inhibiting cocaine-induced motor behaviors. These results suggest that N/OFQ can act directly in the NAc shell to block cocaine-induced increases in extracellular dopamine levels. Extracellular dopamine and locomotor activity can be dissociated within the NAc and may reflect motor output differences in shell versus core regions of the NAc. These studies confirm the widespread involvement of NOP receptors in drug addiction and further validate the utility of an NOP receptor agonist as a medication for treatment of drug addiction. Vazquez-Derose J, Stauber G, Khroyan TV, Xie XS, Zaveri NT, Toll L. Retrodialysis of N/OFQ into the nucleus accumbens shell blocks cocaine-induced increases in extracellular dopamine and locomotor activity. Eur J Pharmacol 2013; 699(1-3): 200-206.

Analysis of Peptides Secreted From Cultured Mouse Brain Tissue Peptides represent a major class of cell-cell signaling molecules. Most peptidomic studies have focused on peptides present in brain or other tissues. For a peptide to function in intercellular signaling, it must be secreted. The present study was undertaken to identify the major peptides secreted from mouse brain slices that were cultured in oxygenated buffer for 3-4h. Approximately 75% of the peptides identified in extracts of cultured slices matched the previously reported peptide content of heat-inactivated mouse brain tissue, whereas only 2% matched the peptide content of unheated brain tissue; the latter showed a large number of postmortem changes. As found with extracts of heat-inactivated mouse brain, the extracts of cultured brain slices represented secretory pathway peptides as well as peptides derived from intracellular proteins such as those present in the cytosol and mitochondria. A subset of the peptides detected in the extracts of the cultured slices was detected in the culture media. The vast majority of secreted peptides arose from intracellular proteins and not secretory pathway proteins. The peptide RVD-hemopressin, a CB1 cannabinoid receptor agonist, was detected in culture media, which is consistent with a role for RVD-hemopressin as a non-classical neuropeptide. Taken together with previous studies, the present results show that short-term culture of mouse brain slices is an appropriate system to study peptide secretion, especially the non-conventional pathway(s) by which peptides produced from intracellular proteins are secreted. This article is part of a Special Issue entitled: An Updated Secretome. Gelman JS, Dasgupta S, Berezniuk I, Fricker LD. Analysis of peptides secreted from cultured mouse brain tissue. Biochim Biophys Acta 2013. Epub ahead of print.

Fluorescent Mu Selective Opioid Ligands From A Mixture Based Cyclic Peptide Library A positional scanning cyclic peptide library was generated using a penta-peptide thioester scaffold. Glycine was fixed at position R(1). Diaminopropionic acid was fixed at position R(3), with its γ-amino attaching to an anthraniloyl group. Positions R(2) and R(4) contained 36 L- and D- amino acids and position R(5) contained 19 L- amino acids. Cyclization was performed in a mixture of acetonitrile and 1.5 M aqueous imidazole solution (7:1 v/v) at room temperature for 5 days. No

significant cross-oligomerization was detected under the cyclization conditions. The library was screened in a binding assay for mu opioid receptor, identifying the active amino acid mixture at each position. A total of 40 individual cyclic peptides were identified and synthesized by the combinations of the most active amino acid mixtures found at three positions 5 × 4 × 2. Two cyclic peptides exhibited high binding affinities to opioid receptor. The most active cyclic peptide in the library was yielded to have Tyr at R(2), D-Lys at R(4), and Tyr at R(5). Further investigation on this compound revealed the side chain-to-tail isomer to have greater binding affinity (14 nM) than the head-to-tail isomer (39 nM). Both isomers were selective for the mu-opioid receptor. Li Y, Dooley CT, Misler JA, Debevec G, Giulianotti MA, Cazares ME, Maida L, Houghten RA. Fluorescent mu selective opioid ligands from a mixture based cyclic peptide library. ACS Comb Sci 2012; 14(12): 673-679.

Individual Differences and Social Influences On The Neurobehavioral Pharmacology Of Abused Drugs The interaction of drugs with biologic targets is a critical area of research, particularly for the development of medications to treat substance use disorders. In addition to understanding these drug-target interactions, however, there is a need to understand more fully the psychosocial influences that moderate these interactions. The first section of this review introduces some examples from human behavioral pharmacology that illustrate the clinical importance of this research. The second section covers preclinical evidence to characterize some of the key individual differences that alter drug sensitivity and abuse vulnerability, related primarily to differences in response to novelty and impulsivity. Evidence is presented to indicate that critical neuropharmacological mechanisms associated with these individual differences involve integrated neurocircuits underlying stress, reward, and behavioral inhibitory processes. The third section covers social influences on drug abuse vulnerability, including effects experienced during infancy, adolescence, and young adulthood, such as maternal separation, housing conditions, and social interactions (defeat, play, and social rank). Some of the same neurocircuits involved in individual differences also are altered by social influences, although the precise neurochemical and cellular mechanisms involved remain to be elucidated fully. Finally, some speculation is offered about the implications of this research for the prevention and treatment of substance abuse. Bardo MT, Neisewander JL, Kelly TH. Individual differences and social influences on the neurobehavioral pharmacology of abused drugs. Pharmacol Rev 2013; 65(1): 255-290.

Regulation Of μ-Opioid Receptors: Desensitization, Phosphorylation, Internalization, and Tolerance Morphine and related μ-opioid receptor (MOR) agonists remain among the most effective drugs known for acute relief of severe pain. A major problem in treating painful conditions is that tolerance limits the long-term utility of opioid agonists. Considerable effort has been expended on developing an understanding of the molecular and cellular processes that underlie acute MOR signaling, short-term receptor regulation, and the progression of events that lead to tolerance for different MOR agonists. Although great progress has been made in the past decade, many points of contention and controversy cloud the realization of this progress. This review attempts to clarify some confusion by clearly defining terms, such as desensitization and tolerance, and addressing optimal pharmacological analyses for discerning relative importance of these cellular mechanisms. Cellular and molecular mechanisms regulating MOR function by phosphorylation relative to receptor desensitization and endocytosis are comprehensively reviewed, with an emphasis on agonist-biased regulation and areas where knowledge is lacking or controversial. The implications of these mechanisms for understanding the substantial contribution of MOR signaling to opioid tolerance are then considered in detail. While some functional MOR regulatory mechanisms contributing to tolerance are clearly understood, there are large gaps in

understanding the molecular processes responsible for loss of MOR function after chronic exposure to opioids. Further elucidation of the cellular mechanisms that are regulated by opioids will be necessary for the successful development of MOR-based approaches to new pain therapeutics that limit the development of tolerance. Williams JT, Ingram SL, Henderson G, Chavkin C, von Zastrow M, Schulz S, Koch T, Evans CJ, Christie MJ. Regulation of μ-opioid receptors: desensitization, phosphorylation, internalization, and tolerance. Pharmacol Rev 2013; 65(1): 223-254.

Targeted Drug Delivery To Treat Pain and Cerebral Hypoxia Limited drug penetration is an obstacle that is often encountered in treatment of central nervous system (CNS) diseases including pain and cerebral hypoxia. Over the past several years, biochemical characteristics of the brain (i.e., tight junction protein complexes at brain barrier sites, expression of influx and efflux transporters) have been shown to be directly involved in determining CNS permeation of therapeutic agents; however, the vast majority of these studies have focused on understanding those mechanisms that prevent drugs from entering the CNS. Recently, this paradigm has shifted toward identifying and characterizing brain targets that facilitate CNS drug delivery. Such targets include the organic anion-transporting polypeptides (OATPs in humans; Oatps in rodents), a family of sodium-independent transporters that are endogenously expressed in the brain and are involved in drug uptake. OATP/Oatp substrates include drugs that are efficacious in treatment of pain and/or cerebral hypoxia (i.e., opioid analgesic peptides, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors). This clearly suggests that OATP/Oatp isoforms are viable transporter targets that can be exploited for optimization of drug delivery to the brain and, therefore, improved treatment of CNS diseases. This review summarizes recent knowledge in this area and emphasizes the potential that therapeutic targeting of OATP/Oatp isoforms may have in facilitating CNS drug delivery and distribution. Additionally, information presented in this review will point to novel strategies that can be used for treatment of pain and cerebral hypoxia. Ronaldson PT, Davis TP. Targeted drug delivery to treat pain and cerebral hypoxia. Pharmacol Rev 2013; 65(1): 291-314.

Integrating Optogenetic and Pharmacological Approaches To Study Neural Circuit Function: Current Applications and Future Directions Optogenetic strategies to control genetically distinct populations of neurons with light have been rapidly evolving and widely adopted by the neuroscience community as one of the most important tool sets to study neural circuit function. Although optogenetics have already reshaped neuroscience by allowing for more precise control of circuit function compared with traditional techniques, current limitations of these approaches should be considered. Here, the authors discuss several strategies that combine optogenetic and contemporary pharmacological techniques to further increase the specificity of neural circuit manipulation. They also discuss recent advances that allow for the selective modulation of cellular function and gene expression with light. In addition, they outline a novel application of optogenetic circuit analysis for causally addressing the role of pathway-specific neural activity in mediating alterations in postsynaptic transcriptional processing in genetically defined neurons. By determining how optogenetic activation of specific neural circuits causally contributes to alterations in gene expression in a high-throughput fashion, novel biologic targets for future pharmacological intervention may be uncovered. Lastly, extending this experimental pipeline to selectively target pharmacotherapies to genetically defined neuronal populations or circuits will not only provide more selective control of neural circuits, but also may lead to the development of neural circuit specific pharmacological therapeutics. Stuber GD, Mason AO. Integrating optogenetic and pharmacological approaches to study neural circuit function: current applications and future directions. Pharmacol Rev 2013; 65(1): 156-170.

The Primate Amygdala Combines Information About Space and Value A stimulus predicting reinforcement can trigger emotional responses, such as arousal, and cognitive ones, such as increased attention toward the stimulus. Neuroscientists have long appreciated that the amygdala mediates spatially nonspecific emotional responses, but it remains unclear whether the amygdala links motivational and spatial representations. To test whether amygdala neurons encode spatial and motivational information, the authors presented reward-predictive cues in different spatial configurations to monkeys and assessed how these cues influenced spatial attention. Cue configuration and predicted reward magnitude modulated amygdala neural activity in a coordinated fashion. Moreover, fluctuations in activity were correlated with trial-to-trial variability in spatial attention. Thus, the amygdala integrates spatial and motivational information, which may influence the spatial allocation of cognitive resources. These results suggest that amygdala dysfunction may contribute to deficits in cognitive processes normally coordinated with emotional responses, such as the directing of attention toward the location of emotionally relevant stimuli. Peck CJ, Lau B, Salzman CD. The primate amygdala combines information about space and value. Nat Neurosci 2013; 16(3): 340-348.

A Chemical Genetic Approach Reveals Distinct Ephb Signaling Mechanisms During Brain Development EphB receptor tyrosine kinases control multiple steps in nervous system development. However, it remains unclear whether EphBs regulate these different developmental processes directly or indirectly. In addition, given that EphBs signal through multiple mechanisms, it has been challenging to define which signaling functions of EphBs regulate particular developmental events. To address these issues, the authors engineered triple knock-in mice in which the kinase activity of three neuronally expressed EphBs can be rapidly, reversibly and specifically blocked. They found that the tyrosine kinase activity of EphBs was required for axon guidance in vivo. In contrast, EphB-mediated synaptogenesis occurred normally when the kinase activity of EphBs was inhibited, suggesting that EphBs mediate synapse development by an EphB tyrosine kinase-independent mechanism. Taken together, these data indicate that EphBs control axon guidance and synaptogenesis by distinct mechanisms and provide a new mouse model for dissecting EphB function in development and disease. Soskis MJ, Ho HYH, Bloodgood BL, Robichaux MA, Malik AN, Ataman B, Rubin AA, Zieg J, Zhang C, Shokat KM, Sharma N, Cowan CW, Greenberg ME. A chemical genetic approach reveals distinct EphB signaling mechanisms during brain development. Nat Neurosci 2012; 15(12): 1645-1654.

New Modules Are Added To Vibrissal Premotor Circuitry With The Emergence Of Exploratory Whisking Rodents begin to use bilaterally coordinated, rhythmic sweeping of their vibrissae ("whisking") for environmental exploration around 2 weeks after birth. Whether (and how) the vibrissal control circuitry changes after birth is unknown, and the relevant premotor circuitry remains poorly characterized. Using a modified rabies virus transsynaptic tracing strategy, the authors labeled neurons synapsing directly onto vibrissa facial motor neurons (vFMNs). Sources of potential excitatory, inhibitory, and modulatory vFMN premotor neurons, and differences between the premotor circuitry for vFMNs innervating intrinsic versus extrinsic vibrissal muscles were systematically characterized. The emergence of whisking is accompanied by the addition of new sets of bilateral excitatory inputs to vFMNs from neurons in the lateral paragigantocellularis (LPGi). Furthermore, descending axons from the motor cortex directly innervate LPGi premotor neurons. Thus, neural modules that are well suited to facilitate the bilateral coordination and cortical control of whisking are added to the premotor circuitry in parallel with the emergence of this exploratory behavior. Takatoh J, Nelson A, Zhou X, Bolton MM, Ehlers MD, Arenkiel BR,

Mooney R, Wang F. New modules are added to vibrissal premotor circuitry with the emergence of exploratory whisking. Neuron 2013; 77(2): 346-360.

Regulation Of Microtubule Stability And Organization By Mammalian Par3 In Specifying Neuronal Polarity Polarization of mammalian neurons with a specified axon requires precise regulation of microtubule and actin dynamics in the developing neurites. Here the authors show that mammalian partition defective 3 (mPar3), a key component of the Par polarity complex that regulates the polarization of many cell types including neurons, directly regulates microtubule stability and organization. The N-terminal portion of mPar3 exhibits strong microtubule binding, bundling, and stabilization activity, which can be suppressed by its C-terminal portion via an intramolecular interaction. Interestingly, the intermolecular oligomerization of mPar3 is able to relieve the intramolecular interaction and thereby promote microtubule bundling and stabilization. Furthermore, disruption of this microtubule regulatory activity of mPar3 impairs its function in axon specification. Together, these results demonstrate a role for mPar3 in directly regulating microtubule organization that is crucial for neuronal polarization. Chen S, Chen J, Shi H, Wei M, Castaneda-Castellanos DR, Bultje RS, Pei X, Kriegstein AR, Zhang M, Shi SH. Regulation of microtubule stability and organization by Mammalian par3 in specifying neuronal polarity. Dev Cell 2013; 24(1): 26-40.

Kinesin-3 Mediates Axonal Sorting and Directional Transport Of Alphaherpesvirus Particles In Neurons During infection of the nervous system, alphaherpesviruses-including pseudorabies virus (PRV)-use retrograde axonal transport to travel toward the neuronal cell body and anterograde transport to traffic back to the cell periphery upon reactivation from latency. The PRV protein Us9 plays an essential but unknown role in anterograde viral spread. To determine Us9 function, the authors identified viral and host proteins that interact with Us9 and explored the role of KIF1A, a microtubule-dependent kinesin-3 motor involved in axonal sorting and transport. Viral particles are cotransported with KIF1A in axons of primary rat superior cervical ganglion neurons, and overexpression or disruption of KIF1A function, respectively, increases and reduces anterograde capsid transport. Us9 and KIF1A interact early during infection with the aid of additional viral protein(s) but exhibit diminished binding at later stages, when capsids typically stall in axons. Thus, alphaherpesviruses repurpose the axonal transport and sorting pathway to spread within their hosts. Kramer T, Greco TM, Taylor MP, Ambrosini AE, Cristea IM, Enquist LW. Kinesin-3 mediates axonal sorting and directional transport of alphaherpesvirus particles in neurons. Cell Host Microbe 2012; 12(6): 806-814.

Nanowire-Mediated Delivery Enables Functional Interrogation Of Primary Immune Cells: Application To The Analysis Of Chronic Lymphocytic Leukemia A circuit level understanding of immune cells and hematological cancers has been severely impeded by a lack of techniques that enable intracellular perturbation without significantly altering cell viability and function. Here, the authors demonstrate that vertical silicon nanowires (NWs) enable gene-specific manipulation of diverse murine and human immune cells with negligible toxicity. To illustrate the power of the technique, the authors then apply NW-mediated gene silencing to investigate the role of the Wnt signaling pathway in chronic lymphocytic leukemia (CLL). Remarkably, CLL-B cells from different patients exhibit tremendous heterogeneity in their response to the knockdown of a single gene, LEF1. This functional heterogeneity defines three distinct patient groups not discernible by conventional CLL cytogenetic markers and provides a prognostic indicator for patients' time to first therapy. Analyses of gene expression signatures associated with these functional patient subgroups reveal unique insights into the underlying molecular basis for disease heterogeneity. Overall, these

findings suggest a functional classification that can potentially guide the selection of patient-specific therapies in CLL and highlight the opportunities for nanotechnology to drive biological inquiry. Shalek AK, Gaublomme JT, Wang L, Yosef N, Chevrier N, Andersen MS, Robinson JT, Pochet N, Neuberg D, Gertner RS, Amit I, Brown JR, Hacohen N, Regev A, Wu CJ, Park H. Nanowire-mediated delivery enables functional interrogation of primary immune cells: application to the analysis of chronic lymphocytic leukemia. Nano Lett 2012; 12(12): 6498-6504.

Probing Enzymatic Activity Inside Living Cells Using A Nanowire-Cell 'Sandwich' Assay

Developing a detailed understanding of enzyme function in the context of an intracellular signal transduction pathway requires minimally invasive methods for probing enzyme activity in situ. Here, the authors describe a new method for monitoring enzyme activity in living cells by sandwiching live cells between two vertical silicon nanowire (NW) arrays. Specifically, they use the first NW array to immobilize the cells and then present enzymatic substrates intracellularly via the second NW array by utilizing the NWs' ability to penetrate cellular membranes without affecting cells' viability or function. This strategy, when coupled with fluorescence microscopy and mass spectrometry, enables intracellular examination of protease, phosphatase, and protein kinase activities, demonstrating the assay's potential in uncovering the physiological roles of various enzymes. Na YR, Kim SY, Gaublomme JT, Shalek AK, Jorgolli M, Park H, Yang EG. Probing enzymatic activity inside living cells using a nanowire-cell 'sandwich' assay. Nano Lett 2013; 13(1): 153-158.

Evidence For A Genetic Component For Substance Dependence In Native Americans

Although tribes differ with regard to the use of alcohol and drugs, substance dependence is one of the primary sources of health problems facing Native Americans. General population studies have demonstrated that substance dependence has a substantially heritable component (approximately 50% of the risk resulting from genetic influences); however, fewer studies have investigated the role of genetics in the risk for substance dependence in Native Americans. The authors present a literature review of the evidence for a genetic component in the etiology of substance dependence in Native Americans, including studies of heritability, linkage analyses, and candidate genes. Evidence for the heritability of alcohol and drug dependence was found. Linkage analyses revealed that genes influencing risk for substance dependence and related phenotypes, such as body mass index (BMI), drug tolerance, EEG patterns, and externalizing traits, reside on several chromosome regions identified in other population samples. Overlap in the gene locations for substance dependence and BMI suggests that a common genetic substrate may exist for disorders of consumption. Studies of the genes that code for alcohol-metabolizing enzymes have not revealed any risk variants specific to Native American populations, although most Native Americans lack protective variants seen in other populations. Other candidate genes associated with substance dependence phenotypes in Native Americans include OPRM1, CRN1, COMT, GABRA2, MAOA, and HTR3-B. The authors conclude that substance dependence has a substantial genetic component in Native Americans, similar in magnitude to that reported for other populations. The high rates of substance dependence seen in some tribes is likely a combination of a lack of genetic protective factors (metabolizing enzyme variants) combined with genetically mediated risk factors (externalizing traits, consumption drive, and drug sensitivity or tolerance) that combine with key environmental factors (trauma exposure, early age at onset of use, and environmental hardship) to produce an elevated risk for the disorder. Ehlers CL, Gizer IR. Evidence for a genetic component for substance dependence in Native Americans. Am J Psychiatry 2013; 170(2): 154-164.

Medications Development for Opioid Abuse Here the authors describe methods for preclinical evaluation of candidate medications to treat opioid abuse and dependence. Their perspective is founded on the propositions that (1) drug self-administration procedures provide the most direct method for assessment of medication effects, (2) procedures that assess choice between opioid and nondrug reinforcers are especially useful, and (3) the states of opioid dependence and withdrawal profoundly influence both opioid reinforcement and the effects of candidate medications. Effects of opioid medications on opioid choice in nondependent and opioid-dependent subjects are reviewed. Various nonopioid medications have also been examined, but none yet have been identified that safely and reliably reduce opioid choice. Future research will focus on (1) strategies for increasing safety and/or effectiveness of opioid medications, and (2) continued development of nonopioids such as inhibitors of endocannabinoid catabolic enzymes or inhibitors of opioid-induced glial activation. Negus SS, Banks ML. Medications development for opioid abuse. Cold Spring Harb Perspect Med 2013; 3(1): a012104.

Psychostimulant-Induced Neuroadaptations In Nucleus Accumbens AMPA Receptor Transmission Medium spiny neurons of the nucleus accumbens serve as the interface between corticolimbic regions that elicit and modulate motivated behaviors, including those related to drugs of abuse, and motor regions responsible for their execution. Medium spiny neurons are excited primarily by AMPA-type glutamate receptors, making AMPA receptor transmission in the accumbens a key regulatory point for addictive behaviors. In animal models of cocaine addiction, changes in the strength of AMPA receptor transmission onto accumbens medium spiny neurons have been shown to underlie cocaine-induced behavioral adaptations related to cocaine seeking. Here the authors review changes in AMPA receptor levels and subunit composition that occur after discontinuing different types of cocaine exposure, as well as changes elicited by cocaine reexposure following abstinence or extinction. Signaling pathways that regulate these cocaine-induced adaptations will also be considered, as they represent potential targets for addiction pharmacotherapies. Pierce RC, Wolf ME. Psychostimulant-induced neuroadaptations in nucleus accumbens AMPA receptor transmission. Cold Spring Harb Perspect Med 2013; 3(2).

Grand Opening Of Structure-Guided Design For Novel Opioids Twelve years after the publication of the first crystal structure of a G-protein-coupled receptor (GPCR), experimental crystal structures of the four opioid receptor subtypes have made their entrance into the literature in the most extraordinary way, that is, all at once. Not only do these crystal structures contribute unprecedented molecular details of opioid ligand binding and specificity, but they also represent important tools for structure-based approaches to guide the discovery of safer and more efficient opioid therapeutics. The authors provide here an overview of these latest breakthroughs in the structural biology of GPCRs with a focus on differences and similarities between the four opioid receptor structures, as well as their limitations, in the context of challenges for translation of this new knowledge from bench to bedside. Filizola M, Devi LA. Grand opening of structure-guided design for novel opioids. Trends Pharmacol Sci 2013; 34(1): 6-12.

The Novel Synaptogenic Protein Farp1 Links Postsynaptic Cytoskeletal Dynamics and Transsynaptic Organization Synaptic adhesion organizes synapses, yet the signaling pathways that drive and integrate synapse development remain incompletely understood. The authors screened for regulators of these processes by proteomically analyzing synaptic membranes lacking the synaptogenic adhesion molecule SynCAM 1. This identified FERM, Rho/ArhGEF, and Pleckstrin domain protein 1 (Farp1) as strongly reduced in SynCAM 1 knockout mice. Farp1 regulates dendritic filopodial dynamics in immature neurons, indicating roles in synapse formation.

Later in development, Farp1 is postsynaptic and its 4.1 protein/ezrin/radixin/moesin (FERM) domain binds SynCAM 1, assembling a synaptic complex. Farp1 increases synapse number and modulates spine morphology, and SynCAM 1 requires Farp1 for promoting spines. In turn, SynCAM 1 loss reduces the ability of Farp1 to elevate spine density. Mechanistically, Farp1 activates the GTPase Rac1 in spines downstream of SynCAM 1 clustering, and promotes F-actin assembly. Farp1 furthermore triggers a retrograde signal regulating active zone composition via SynCAM 1. These results reveal a postsynaptic signaling pathway that engages transsynaptic interactions to coordinate synapse development. Cheadle L, Biederer T. The novel synaptogenic protein Farp1 links postsynaptic cytoskeletal dynamics and transsynaptic organization. J Cell Biol 2012; 199(6): 985-1001.

Ptdins4p Synthesis By PI4KIIIα At the Plasma Membrane and Its Impact On Plasma Membrane Identity Plasma membrane phosphatidylinositol (PI) 4-phosphate (PtdIns4P) has critical functions via both direct interactions and metabolic conversion to PI 4,5-bisphosphate (PtdIns(4,5)P_2) and other downstream metabolites. However, mechanisms that control this PtdIns4P pool in cells of higher eukaryotes remain elusive. PI4KIIIα, the enzyme thought to synthesize this PtdIns4P pool, is reported to localize in the ER, contrary to the plasma membrane localization of its yeast homologue, Stt4. In this paper, the authors show that PI4KIIIα was targeted to the plasma membrane as part of an evolutionarily conserved complex containing Efr3/rolling blackout, which they found was a palmitoylated peripheral membrane protein. PI4KIIIα knockout cells exhibited a profound reduction of plasma membrane PtdIns4P but surprisingly only a modest reduction of PtdIns(4,5)P_2 because of robust up-regulation of PtdIns4P 5-kinases. In these cells, however, much of the PtdIns(4,5)P_2 was localized intracellularly, rather than at the plasma membrane as in control cells, along with proteins typically restricted to this membrane, revealing a major contribution of PI4KIIIα to the definition of plasma membrane identity. Nakatsu F, Baskin JM, Chung J, Tanner LB, Shui G, Lee SY, Pirruccello M, Hao M, Ingolia NT, Wenk MR, De Camilli P. PtdIns4P synthesis by PI4KIIIα at the plasma membrane and its impact on plasma membrane identity. J Cell Biol 2012; 199(6): 1003-1016.

Munc13 Controls The Location And Efficiency Of Dense-Core Vesicle Release In Neurons Neuronal dense-core vesicles (DCVs) contain diverse cargo crucial for brain development and function, but the mechanisms that control their release are largely unknown. The authors quantified activity-dependent DCV release in hippocampal neurons at single vesicle resolution. DCVs fused preferentially at synaptic terminals. DCVs also fused at extrasynaptic sites but only after prolonged stimulation. In munc13-1/2-null mutant neurons, synaptic DCV release was reduced but not abolished, and synaptic preference was lost. The remaining fusion required prolonged stimulation, similar to extrasynaptic fusion in wild-type neurons. Conversely, Munc13-1 overexpression (M13OE) promoted extrasynaptic DCV release, also without prolonged stimulation. Thus, Munc13-1/2 facilitate DCV fusion but, unlike for synaptic vesicles, are not essential for DCV release, and M13OE is sufficient to produce efficient DCV release extrasynaptically. van de Bospoort R, Farina M, Schmitz SK, de Jong A, de Wit H, Verhage M, Toonen RF. Munc13 controls the location and efficiency of dense-core vesicle release in neurons. J Cell Biol 2012; 199(6): 883-891.

Action Control Is Mediated By Prefrontal BDNF and Glucocorticoid Receptor Binding Stressor exposure biases decision-making strategies from those based on the relationship between actions and their consequences to others restricted by stimulus-response associations. Chronic stressor exposure also desensitizes glucocorticoid receptors (GR) and diminishes motivation to acquire food reinforcement, although causal relationships are largely not established. The authors

show that a history of chronic exposure to the GR ligand corticosterone or acute posttraining GR blockade with RU38486 makes rodents less able to perform actions based on their consequences. Thus, optimal GR binding is necessary for the consolidation of new response-outcome learning. In contrast, medial prefrontal (but not striatal) BDNF can account for stress-related amotivation, in that selective medial prefrontal cortical Bdnf knockdown decreases break-point ratios in a progressive-ratio task. Knockdown also increases vulnerability to RU38486. Despite the role of BDNF in dendritic spine reorganization, deep-layer spine remodeling does not obviously parallel progressive-ratio response patterns, but treatment with the Na(+)-channel inhibitor riluzole reverses corticosteroid-induced motivational deficits and restores prefrontal BDNF expression after corticosterone. The authors argue that when prefrontal neurotrophin systems are compromised, and GR-mediated hypothalamic-pituitary-adrenal axis feedback is desensitized (as in the case of chronic stress hormone exposure), amotivation and inflexible maladaptive response strategies that contribute to stress-related mood disorders result. Gourley SL, Swanson AM, Jacobs AM, Howell JL, Mo M, Dileone RJ, Koleske AJ, Taylor JR. Action control is mediated by prefrontal BDNF and glucocorticoid receptor binding. Proc Natl Acad Sci U S A 2012; 109(50); 20714-20719.

Structural Elements In The Girk1 Subunit That Potentiate G Protein-Gated Potassium Channel Activity G protein-gated inwardly rectifying K(+) (Girk/K(IR)3) channels mediate the inhibitory effect of many neurotransmitters on excitable cells. Girk channels are tetramers consisting of various combinations of four mammalian Girk subunits (Girk1 to -4). Although Girk1 is unable to form functional homomeric channels, its presence in cardiac and neuronal channel complexes correlates with robust channel activity. This study sought to better understand the potentiating influence of Girk1, using the GABA(B) receptor and Girk1/Girk2 heteromer as a model system. Girk1 did not increase the protein levels or alter the trafficking of Girk2-containing channels to the cell surface in transfected cells or hippocampal neurons, indicating that its potentiating influence involves enhancement of channel activity. Structural elements in both the distal carboxyl-terminal domain and channel core were identified as key determinants of robust channel activity. In the distal carboxyl-terminal domain, residue Q404 was identified as a key determinant of receptor-induced channel activity. In the Girk1 core, three unique residues in the pore (P) loop (F137, A142, Y150) were identified as a collective potentiating influence on both receptor-dependent and receptor-independent channel activity, exerting their influence, at least in part, by enhancing mean open time and single-channel conductance. Interestingly, the potentiating influence of the Girk1 P-loop is tempered by residue F162 in the second membrane-spanning domain. Thus, discontinuous and sometime opposing elements in Girk1 underlie the Girk1-dependent potentiation of receptor-dependent and receptor-independent heteromeric channel activity. Wydeven N, Young D, Mirkovic K, Wickman K. Structural elements in the Girk1 subunit that potentiate G protein-gated potassium channel activity. Proc Natl Acad Sci U S A 2012; 109(52): 21492-21497.

Nerve Growth Factor Scales Endocannabinoid Signaling By Regulating Monoacylglycerol Lipase Turnover In Developing Cholinergic Neurons Endocannabinoid, particularly 2-arachidonoyl glycerol (2-AG), signaling has recently emerged as a molecular determinant of neuronal migration and synapse formation during cortical development. However, the cell type specificity and molecular regulation of spatially and temporally confined morphogenic 2-AG signals remain unexplored. Here, the authors demonstrate that genetic and pharmacological manipulation of CB(1) cannabinoid receptors permanently alters cholinergic projection neuron identity and hippocampal innervation. They show that nerve growth factor (NGF), implicated in the morphogenesis and survival of cholinergic projection neurons, dose-dependently and coordinately

regulates the molecular machinery for 2-AG signaling via tropomyosine kinase A receptors in vitro. In doing so, NGF limits the sorting of monoacylglycerol lipase (MGL), rate limiting 2-AG bioavailability, to proximal neurites, allowing cell-autonomous 2-AG signaling at CB(1) cannabinoid receptors to persist at atypical locations to induce superfluous neurite extension. The authors find that NGF controls MGL degradation in vitro and in vivo and identify the E3 ubiquitin ligase activity of breast cancer type 1 susceptibility protein (BRCA1) as a candidate facilitating MGL's elimination from motile neurite segments, including growth cones. BRCA1 inactivation by cisplatin or genetically can rescue and reposition MGL, arresting NGF-induced growth responses. These data indicate that NGF can orchestrate endocannabinoid signaling to promote cholinergic differentiation and implicate BRCA1 in determining neuronal morphology. Keimpema E, Tortoriello G, Alpar A, Capsoni S, Arisi I, Calvigioni D, Hu SSJ, Cattaneo A, Doherty P, Mackie K, Harkany T. Nerve growth factor scales endocannabinoid signaling by regulating monoacylglycerol lipase turnover in developing cholinergic neurons. Proc Natl Acad Sci U S A 2013; 110(5): 1935-1940.

A Dictionary Of Behavioral Motifs Reveals Clusters Of Genes Affecting Caenorhabditis Elegans Locomotion Visible phenotypes based on locomotion and posture have played a critical role in understanding the molecular basis of behavior and development in Caenorhabditis elegans and other model organisms. However, it is not known whether these human-defined features capture the most important aspects of behavior for phenotypic comparison or whether they are sufficient to discover new behaviors. Here the authors show that four basic shapes, or eigenworms, previously described for wild-type worms, also capture mutant shapes, and that this representation can be used to build a dictionary of repetitive behavioral motifs in an unbiased way. By measuring the distance between each individual's behavior and the elements in the motif dictionary, the authors create a fingerprint that can be used to compare mutants to wild type and to each other. This analysis has revealed phenotypes not previously detected by real-time observation and has allowed clustering of mutants into related groups. Behavioral motifs provide a compact and intuitive representation of behavioral phenotypes. Brown AEX, Yemini EI, Grundy LJ, Jucikas T, Schafer WR. A dictionary of behavioral motifs reveals clusters of genes affecting Caenorhabditis elegans locomotion. Proc Natl Acad Sci U S A 2013; 110(2): 791-796.

Functional Characterization Of Piggybat From The Bat Myotis Lucifugus Unveils An Active Mammalian DNA Transposon A revelation of the genomic age has been the contributions of the mobile DNA segments called transposable elements to chromosome structure, function, and evolution in virtually all organisms. Substantial fractions of vertebrate genomes derive from transposable elements, being dominated by retroelements that move via RNA intermediates. Although many of these elements have been inactivated by mutation, several active retroelements remain. Vertebrate genomes also contain substantial quantities and a high diversity of cut-and-paste DNA transposons, but no active representative of this class has been identified in mammals. Here the authors show that a cut-and-paste element called piggyBat, which has recently invaded the genome of the little brown bat (Myotis lucifugus) and is a member of the piggyBac superfamily, is active in its native form in transposition assays in bat and human cultured cells, as well as in the yeast Saccharomyces cerevisiae. This study suggests that some DNA transposons are still actively shaping some mammalian genomes and reveals an unprecedented opportunity to study the mechanism, regulation, and genomic impact of cut-and-paste transposition in a natural mammalian host. Mitra R, Li X, Kapusta A, Mayhew D, Mitra RD, Feschotte C, Craig NL. Functional characterization of piggyBat from the bat Myotis lucifugus unveils an active mammalian DNA transposon. Proc Natl Acad Sci U S A 2013; 110(1): 234-239.

Mirtazapine, and Mirtazapine-Like Compounds As Possible Pharmacotherapy For Substance Abuse Disorders: Evidence From The Bench and The Bedside Understanding substance use disorders (SUDs) and the problems associated with abstinence has grown in recent years. Nonetheless, highly efficacious treatment targeting relapse prevention has remained elusive, and there remains no FDA-approved pharmacotherapy for psychostimulant dependence. Preclinical and clinical investigations assessing the utility of classical antidepressants, which block monoamine reuptake, show mixed and often contradictory results. Mirtazapine (Remeron®) is a unique FDA-approved antidepressant, with negligible affinity for reuptake proteins, indirectly augments monoamine transmission presumably through antagonist activity at multiple receptors including the norepinephrine (NE)(α2), and serotonin (5-HT)(2A/C) receptors. Historically, mirtazapine was also considered to be a 5-HT(2C) antagonist, but recent evidence indicates that mirtazapine is an inverse agonist at this receptor subtype. Suggesting a promising role for mixed-action serotonergic drugs for addiction pharmacotherapy, mirtazapine attenuates psychostimulant-induced behaviors in several rodent models of substance abuse, and antagonizes methamphetamine-induced biochemical and electrophysiological alterations in rats. Preclinical findings are confirmed through published case studies documenting successful outcomes with mirtazapine therapy across a number of SUDs. To date, a large scale clinical trial assessing the utility of mirtazapine in substance abuse pharmacotherapy has yet to be conducted. However, as reviewed here, accumulating preclinical and clinical evidence argues that mirtazapine, or compounds that emulate aspects of its pharmacological profile, may prove useful in helping treat addictions. Graves SM, Rafeyan R, Watts J, Napier TC. Mirtazapine, and mirtazapine-like compounds as possible pharmacotherapy for substance abuse disorders: evidence from the bench and the bedside. Pharmacol Ther 2012; 136(3): 343-353.

Attention-Related Pearce-Kaye-Hall Signals In Basolateral Amygdala Require the Midbrain Dopaminergic System Neural activity in basolateral amygdala has recently been shown to reflect surprise or attention as predicted by the Pearce-Kaye-Hall model (PKH)--an influential model of associative learning. Theoretically, a PKH attentional signal originates in prediction errors of the kind associated with phasic firing of dopamine neurons. This requirement for prediction errors, coupled with projections from the midbrain dopamine system into basolateral amygdala, suggests that the PKH signal in amygdala may depend on dopaminergic input. To test this, the authors recorded single unit activity in basolateral amygdala in rats with 6-hydroxydopamine or sham lesions of the ipsilateral midbrain region. Neurons were recorded as the rats performed a task previously used to demonstrate both dopaminergic reward prediction errors and attentional signals in basolateral amygdala neurons. The authors found that neurons recorded in sham lesioned rats exhibited the same attention-related PKH signal observed in previous studies. By contrast, neurons recorded in rats with ipsilateral 6-hydroxydopamine lesions failed to show attentional signaling. These results indicate a linkage between the neural instantiations of the basolateral complex of the amygdala attentional signal and dopaminergic prediction errors. Such a linkage would have important implications for understanding both normal and aberrant learning and behavior, particularly in diseases thought to have a primary effect on dopamine systems, such as addiction and schizophrenia. Esber GR, Roesch MR, Bali S, Trageser J, Bissonette GB, Puche AC, Holland PC, Schoenbaum G. Attention-related pearce-kaye-Hall signals in basolateral amygdala require the midbrain dopaminergic system. Biol Psychiatry 2012; 72(12): 1012-1019.

Prefrontal Cortex Modulates Desire And Dread Generated By Nucleus Accumbens Glutamate Disruption Corticolimbic circuits, including direct projections from prefrontal cortex to nucleus accumbens (NAc), permit top-down control of intense motivations generated by subcortical circuits. In rats, localized disruptions of glutamate signaling within medial shell of NAc generate desire or

dread, anatomically organized along a rostrocaudal gradient analogous to a limbic keyboard. At rostral locations in shell, these disruptions generate appetitive eating, but at caudal locations the disruptions generate progressively fearful behaviors (distress vocalizations, escape attempts, and antipredator reactions). Here, the authors asked whether medial prefrontal cortex can modulate intense motivations generated by subcortical NAc disruptions. They used simultaneous microinjections in medial prefrontal cortex regions and in NAc shell to examine whether the desire or dread generated by NAc shell disruptions is modulated by activation/inhibition of three specific regions of prefrontal cortex: medial orbitofrontal cortex, infralimbic cortex (homologous to area 25 or subgenual anterior cingulate in the human), or prelimbic cortex (midventral anterior cingulate). They found that activation of medial orbitofrontal cortex biased intense bivalent motivation in an appetitive direction by amplifying generation of eating behavior by middle to caudal NAc disruptions, without altering fear. In contrast, activation of infralimbic prefrontal cortex powerfully and generally suppressed both appetitive eating and fearful behaviors generated by NAc shell disruptions. These results suggest that corticolimbic projections from discrete prefrontal regions can either bias motivational valence or generally suppress subcortically generated intense motivations of desire or fear. Richard JM, Berridge KC. Prefrontal cortex modulates desire and dread generated by nucleus accumbens glutamate disruption. Biol Psychiatry 2013; 73(4): 360-370.

Synaptic Dysfunction In The Hippocampus Accompanies Learning and Memory Deficits In Human Immunodeficiency Virus Type-1 Tat Transgenic Mice Human immunodeficiency virus (HIV) associated neurocognitive disorders (HAND), including memory dysfunction, continue to be a major clinical manifestation of HIV type-1 infection. Viral proteins released by infected glia are thought to be the principal triggers of inflammation and bystander neuronal injury and death, thereby driving key symptomatology of HAND. The authors used a glial fibrillary acidic protein-driven, doxycycline-inducible HIV type-1 transactivator of transcription (Tat) transgenic mouse model and examined structure-function relationships in hippocampal pyramidal cornu ammonis 1 (CA1) neurons using morphologic, electrophysiological (long-term potentiation [LTP]), and behavioral (Morris water maze, fear-conditioning) approaches. RESULTS: Tat induction caused a variety of different inclusions in astrocytes characteristic of lysosomes, autophagic vacuoles, and lamellar bodies, which were typically present within distal cytoplasmic processes. In pyramidal CA1 neurons, Tat induction reduced the number of apical dendritic spines, while disrupting the distribution of synaptic proteins (synaptotagmin 2 and gephyrin) associated with inhibitory transmission but with minimal dendritic pathology and no evidence of pyramidal neuron death. Electrophysiological assessment of excitatory postsynaptic field potential at Schaffer collateral/commissural fiber-CA1 synapses showed near total suppression of LTP in mice expressing Tat. The loss in LTP coincided with disruptions in learning and memory. Tat expression in the brain results in profound functional changes in synaptic physiology and in behavior that are accompanied by only modest structural changes and minimal pathology. Tat likely contributes to HAND by causing molecular changes that disrupt synaptic organization, with inhibitory presynaptic terminals containing synaptotagmin 2 appearing especially vulnerable. Fitting S, Ignatowska-Jankowska BM, Bull C, Skoff RP, Lichtman AH, Wise LE, Fox MA, Su J, Medina AE, Krahe TE, Knapp PE, Guido W, Hauser KF. Synaptic dysfunction in the hippocampus accompanies learning and memory deficits in human immunodeficiency virus type-1 tat transgenic mice. Biol Psychiatry 2013; 73(5): 443-453.

Psychiatric Drugs Bind To Classical Targets Within Early Exocytotic Pathways: Therapeutic Effects The classical targets for antipsychotic and antidepressant drugs are G protein-coupled receptors and neurotransmitter transporters, respectively. Full therapeutic actions of these drugs require several weeks. The authors show how therapeutic effects may eventually accrue after existing therapeutic ligands bind to these classical targets, not on the plasma membrane but rather within endoplasmic reticulum (ER) and cis-Golgi. Consequences of such binding may include pharmacological chaperoning: the nascent drug targets are stabilized against degradation and can therefore exit the ER more readily. Another effect may be matchmaking: heterodimers and homodimers of the target form and can more readily exit the ER. Summarizing recent data for nicotinic receptors, the authors explain how such effects could lead to reduced ER stress and to a decreased unfolded protein response, including changes in gene activation and protein synthesis. In effects not directly related to cellular stress, escorting would allow increased ER exit and trafficking of known associated proteins, as well as other proteins such as growth factors and their receptors, producing both cell-autonomous and non-cell-autonomous effects. Axonal transport of relevant proteins may underlie the several weeks required for full therapy. In contrast, the antidepressant effects of ketamine and other N-methyl-D-aspartate receptor ligands, which occur within <2 hours, could arise from dendritically localized intracellular binding, followed by chaperoning, matchmaking, escorting, and reduced ER stress. Thus, the effects of intracellular binding extend beyond proteostasis of the targets themselves and involve pathways distinct from ion channel and G protein activation. The authors propose experimental tests and note pathophysiological correlates. Lester HA, Miwa JM, Srinivasan R. Psychiatric drugs bind to classical targets within early exocytotic pathways: therapeutic effects. Biol Psychiatry 2012; 72(11): 907-915.

Phasic Mesolimbic Dopamine Release Tracks Reward Seeking During Expression of Pavlovian-to-Instrumental Transfer Recent theories addressing mesolimbic dopamine's role in reward processing emphasize two apparently distinct functions, one in reinforcement learning (i.e., prediction error) and another in incentive motivation (i.e., the invigoration of reward seeking elicited by reward-paired cues). Here, the authors evaluate the latter. Using fast-scan cyclic voltammetry, they monitored, in real time, dopamine release in the nucleus accumbens core of rats (n = 9) during a Pavlovian-to-instrumental transfer task in which the effects of a reward-predictive cue on an independently trained instrumental action were assessed. Voltammetric data were parsed into slow and phasic components to determine whether these forms of dopamine signaling were differentially related to task performance. They found that a reward-paired cue, which increased reward-seeking actions, induced an increase in phasic mesolimbic dopamine release and produced slower elevations in extracellular dopamine. Interestingly, phasic dopamine release was temporally related to and positively correlated with lever-press activity generally, while slow dopamine changes were not significantly related to such activity. Importantly, the propensity of the reward-paired cue to increase lever pressing was predicted by the amplitude of phasic dopamine release events, indicating a possible mechanism through which cues initiate reward-seeking actions. These data suggest that those phasic mesolimbic dopamine release events thought to signal reward prediction error may also be related to the incentive motivational impact of reward-paired cues on reward-seeking actions. Wassum KM, Ostlund SB, Loewinger GC, Maidment NT. Phasic Mesolimbic Dopamine Release Tracks Reward Seeking During Expression of Pavlovian-to-Instrumental Transfer. Biol Psychiatry 2013. Epub ahead of print.

Opposing Catecholamine Changes in the Bed Nucleus of the Stria Terminalis During Intracranial Self-Stimulation and Its Extinction While studies suggest that both dopamine and norepinephrine neurotransmission support reinforcement learning, the role of dopamine has been emphasized. As a result, little is known about norepinephrine signaling during reward learning and extinction. Both dopamine and norepinephrine projections innervate distinct regions of the bed nucleus of the stria terminalis (BNST), a structure that mediates behavioral and autonomic responses to stress and anxiety. The authors investigated whether norepinephrine release in the ventral BNST (vBNST) and dopamine release in the dorsolateral BNST (dlBNT) correlate with reward learning during intracranial self-stimulation (ICSS). Using fast-scan cyclic voltammetry, norepinephrine concentration changes in the vBNST (n = 12 animals) during ICSS were compared with dopamine changes in the dlBNST (n = 7 animals) and nucleus accumbens (NAc) (n = 5 animals). Electrical stimulation was in the ventral tegmental area/substantia nigra region. Whereas dopamine release was evoked by presentation of a cue predicting reward availability in both dlBNST and NAc, cue-evoked norepinephrine release did not occur in the vBNST. Release of both catecholamines was evoked by the electrical stimulation. Extracellular changes in norepinephrine were also studied during extinction of ICSS and compared with results obtained for dopamine. During extinction of ICSS, norepinephrine release in the vBNST occurred at the time where the stimulation was anticipated, whereas dopamine release transiently decreased. The data demonstrate that norepinephrine release in the vBNST differs from dopamine release in the dlBNST and the NAc in that it signals the absence of reward rather than responding to reward predictive cues. Park J, Bucher ES, Fontillas K, Owesson-White C, Ariansen JL, Carelli RM, Wightman RM. Opposing Catecholamine Changes in the Bed Nucleus of the Stria Terminalis During Intracranial Self-Stimulation and Its Extinction. Biol Psychiatry 2012. Epub ahead of print.

Reinforcing Effects Of Compounds Lacking Intrinsic Efficacy At α1 Subunit-Containing GABA(A) Receptor Subtypes in Midazolam- But Not Cocaine-Experienced Rhesus Monkeys Benzodiazepines are prescribed widely but their utility is limited by unwanted side effects, including abuse potential. The mechanisms underlying the abuse-related effects of benzodiazepines are not well understood, although α1 subunit-containing GABA(A) receptors have been proposed to have a critical role. Here, the authors examine the reinforcing effects of several compounds that vary with respect to intrinsic efficacy at α2, α3, and α5 subunit-containing GABA(A) receptors but lack efficacy at α1 subunit-containing GABA(A) receptors ('α1-sparing compounds'): MRK-623 (functional selectivity for α2/α3 subunit-containing receptors), TPA023B (functional selectivity for α2/α3/α5 subunit-containing receptors), and TP003 (functional selectivity for α3 subunit-containing receptors). The reinforcing effects of the α1-sparing compounds were compared with those of the non-selective benzodiazepine receptor partial agonist MRK-696, and non-selective benzodiazepine receptor full agonists, midazolam and lorazepam, in rhesus monkeys trained to self-administer midazolam or cocaine, under a progressive-ratio schedule of intravenous (i.v.) drug injection. The α1-sparing compounds were self-administered significantly above vehicle levels in monkeys maintained under a midazolam baseline, but not under a cocaine baseline over the dose ranges tested. Importantly, TP003 had significant reinforcing effects, albeit at lower levels of self-administration than non-selective benzodiazepine receptor agonists. Together, these results suggest that α1 subunit-containing GABA(A) receptors may have a role in the reinforcing effects of benzodiazepine-type compounds in monkeys with a history of stimulant self-administration, whereas α3 subunit-containing GABA(A) receptors may be important mediators of the reinforcing effects of benzodiazepine-type compounds in animals with a history of sedative-anxiolytic/benzodiazepine self-administration.Neuropsychopharmacology advance online publication, 16 January 2013; doi:10.1038/npp.2012.265. Shinday NM, Sawyer EK, Fischer BD;

Platt DM, Licata SC, Atack JR, Dawson GR, Reynolds DS, Rowlett JK. Reinforcing Effects Of Compounds Lacking Intrinsic Efficacy At α1 Subunit-Containing GABA(A) Receptor Subtypes in Midazolam- But Not Cocaine-Experienced Rhesus Monkeys. Neuropsychopharmacology 2012. Epub ahead of print.

Glycine Transporter-1 Inhibition Preceding Extinction Training Inhibits Reacquisition Of Cocaine Seeking Cognitive enhancers that act by increasing glycine transmission might be useful adjuncts to cocaine-cue extinction training to deter relapse. The study investigated the effects of combining treatments of the glycine transporter-1 (GlyT-1) inhibitor, Org24598, with extinction training on the subsequent reacquisition of cocaine self-administration. Squirrel monkeys and rats were trained to self-administer cocaine under a second-order schedule of intravenous drug injection in which responding was maintained by cocaine injections and a cocaine-paired visual stimulus. During three weekly extinction sessions, saline was substituted for cocaine but responding still produced the cocaine-paired stimulus. Subjects were treated with Org24598 or vehicle, either before or after each extinction session. One week later, cocaine injections were restored, and reacquisition of cocaine self-administration was evaluated over 15 sessions. Compared with vehicle, administration of Org24598 (1.0 mg/kg in monkeys; 3.0 or 7.5 mg/kg in rats) before each extinction session significantly inhibited reacquisition of cocaine self-administration in each species. In contrast, administration of Org24598 (1.0 mg/kg in monkeys) following, rather than preceding, each extinction session did not affect reacquisition compared with vehicle. When extinction training was replaced by cocaine self-administration or abstinence control conditions, treatment with the same doses of Org24598 resulted in reacquisition that was significantly more rapid than the reacquisition observed when Org24598 was administered before extinction training sessions. The results support the potential clinical utility of GlyT-1 inhibitor pretreatments combined with cocaine-cue extinction training to inhibit relapse. Achat-Mendes C, Nic Dhonnchadha BA, Platt DM, Kantak KM, Spealman RD. Glycine transporter-1 inhibition preceding extinction training inhibits reacquisition of cocaine seeking. Neuropsychopharmacology 2012; 37(13): 2837-2845.

Pain after Discontinuation of Morphine Treatment is Associated with Synaptic Increase of GluA4-Containing AMPAR in the Dorsal Horn of the Spinal Cord Withdrawal from prescribed opioids results in increased pain sensitivity, which prolongs the treatment. This pain sensitivity is attributed to neuroplastic changes that converge at the spinal cord dorsal horn. The authors have recently reported that repeated morphine administration triggers an insertion of GluA2-lacking (Ca^{2+}-permeable) α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPAR) in the hippocampus. This finding together with the reported involvement of AMPAR in the mechanisms underlying inflammatory pain led us to hypothesize a role for spinal AMPAR in opioid-induced pain behavior. Mice treated with escalating doses of morphine showed hypersensitivity to mechanical stimulation. Intrathecal administration of a Ca^{2+}-permeable AMPAR selective blocker disrupted morphine-induced mechanical sensitivity. Analysis of the expression and phosphorylation levels of AMPAR subunits (GluA1/2/3/4) in homogenates and in postsynaptic density fractions from spinal cord dorsal horns showed an increase in GluA4 expression and phosphorylation in the postsynaptic density after morphine. Co-immunoprecipitation analyses suggested an increase in GluA4 homomers (Ca^{2+}-permeable AMPAR) and immunohistochemical staining localized the increase in GluA4 levels in laminae III-V. The excitatory postsynaptic currents (EPSCs) recorded in laminae III-V showed enhanced sensitivity to Ca^{2+}-permeable AMPAR blockers in morphine-treated mice. Furthermore, current-voltage relationships of AMPAR-mediated EPSCs showed that rectification index (an indicator of Ca^{2+}-permeable AMPAR contribution) is increased in morphine-treated but not in saline-treated mice. These effects could be

reversed by infusion of GluA4 antibody through patch pipette. This is the first direct evidence for a role of GluA4-containing AMPAR in morphine-induced pain and highlights spinal GluA4-containing AMPAR as targets to prevent the morphine-induced pain sensitivity. Neuropsychopharmacology advance online publication, 6 March 2013; Cabanero D, Baker A, Zhou S, Hargett GL, Irie T, Xia Y, Beaudry H, Gendron L, Melyan Z, Carlton SM, Moron JA. Pain after discontinuation of morphine treatment is associated with synaptic increase of Glua4-containing ampar in the dorsal horn of the spinal cord. Neuropsychopharmacology 2013. Epub ahead of print.

An Evaluation Of the Evidence That Methamphetamine Abuse Causes Cognitive Decline In Humans Methamphetamine (MA) is one of the most commonly abused illicit substances worldwide. Among other problems, abuse of the drug has been associated with reduced cognitive function across several domains. However, much of the literature has not attempted to differentiate cognitive difficulties caused by MA abuse from preexisting cognitive difficulties that are likely caused by other factors. Here, the authors address this question, evaluating evidence for a priori hypotheses pertaining to six lines of research: (a) animal studies; (b) cross-sectional human studies; (c) a twin study; (d) studies of changes in cognition with abstinence from MA; (e) studies of changes in brain structure and function with abstinence from MA; and (f) studies of the relationship between the severity of MA abuse and the extent of cognitive deficits observed. Overall the findings were mixed, with some support for a causal relationship between MA abuse and cognitive decline, and other findings suggesting that there is no relationship. The preponderance of the data, however, does support the possibility that MA abuse causes cognitive decline, of unknown duration, in at least some users of the drug. When averaged across individuals, this decline is likely to be mild in early-to-middle adulthood. However, moderator variables are likely to contribute to the presence and/or severity of cognitive decline exhibited by a given individual. Dean AC, Groman SM, Morales AM, London ED. An evaluation of the evidence that methamphetamine abuse causes cognitive decline in humans. Neuropsychopharmacology 2013; 38(2): 259-274.

Clozapine-Induced Locomotor Suppression Is Mediated By 5-HT(2A) Receptors In the Forebrain The need for safer, more effective therapeutics for the treatment of schizophrenia is widely acknowledged. To optimally target novel pharmacotherapies, in addition to establishing the mechanisms responsible for the beneficial effects of antipsychotics, the pathways underlying the most severe side effects must also be elucidated. Here the authors investigate the role of serotonin 2A (5-HT(2A)), serotonin 2C (5-HT(2C)), and dopamine 2 receptors (D_2) in mediating adverse effects associated with canonical first- and second-generation antipsychotic drugs in mice. Wild-type (WT) and 5-HT(2A) knockout (KO) mice treated with haloperidol, clozapine, and risperidone were assessed for locomotor activity and catalepsy. WT mice showed a marked reduction in locomotor activity following acute administration of haloperidol and high-dose risperidone, which was most likely secondary to the severe catalepsy caused by these compounds. Clozapine also dramatically reduced locomotor activity, but in the absence of catalepsy. Interestingly, 5-HT(2A) KO mice were cataleptic following haloperidol and risperidone, but did not respond to clozapine's locomotor-suppressing effects. Restoration of 5-HT(2A) expression to cortical glutamatergic neurons re-instated the locomotor-suppressing effects of clozapine in the open field. In sum, the authors confirm that haloperidol and risperidone caused catalepsy in rodents, driven by strong antagonism of D_2. They also demonstrate that clozapine decreases locomotor activity in a 5-HT(2A)-dependent manner, in the absence of catalepsy. Moreover, they show that it is the cortical population of 5-HT(2A) that mediate the locomotor-suppressing effects of clozapine. McOmish CE, Lira A, Hanks JB, Gingrich JA. Clozapine-induced locomotor suppression is mediated by 5-HT(2A) receptors in the forebrain. Neuropsychopharmacology 2012; 37(13): 2747-2755.

The Volitional Nature Of Nicotine Exposure Alters Anandamide and Oleoylethanolamide Levels In the Ventral Tegmental Area Cannabinoid-1 receptors (CB(1)) have an important role in nicotine reward and their function is disrupted by chronic nicotine exposure, suggesting nicotine-induced alterations in endocannabinoid (eCB) signaling. However, the effects of nicotine on brain eCB levels have not been rigorously evaluated. Volitional intake of nicotine produces physiological and behavioral effects distinct from forced drug administration, although the mechanisms underlying these effects are not known. This study compared the effects of volitional nicotine self-administration (SA) and forced nicotine exposure (yoked administration (YA)) on levels of eCBs and related neuroactive lipids in the ventral tegmental area (VTA) and other brain regions. Brain lipid levels were indexed both by in vivo microdialysis in the VTA and lipid extractions from brain tissues. Nicotine SA, but not YA, reduced baseline VTA dialysate oleoylethanolamide (OEA) levels relative to nicotine-naïve controls, and increased anandamide (AEA) release during nicotine intake. In contrast, all nicotine exposure paradigms increased VTA dialysate 2-arachidonoyl glycerol (2-AG) levels. Thus, nicotine differentially modulates brain lipid (2-AG, AEA, and OEA) signaling, and these modulations are influenced by the volitional nature of the drug exposure. Corresponding bulk tissue analysis failed to identify these lipid changes. Nicotine exposure had no effect on fatty acid amide hydrolase activity in the VTA, suggesting that changes in AEA and OEA signaling result from alterations in their nicotine-induced biosynthesis. Both CB(1) (by AEA and 2-AG) and non-CB(1) (by OEA) targets can alter the excitability and activity of the dopaminergic neurons in the VTA. Collectively, these findings implicate disrupted lipid signaling in the motivational effects of nicotine. Buczynski MW, Polis IY, Parsons LH. The volitional nature of nicotine exposure alters anandamide and oleoylethanolamide levels in the ventral tegmental area. Neuropsycho-pharmacology 2013; 38(4): 574-584.

Seizure Susceptibility and Epileptogenesis In A Rat Model Of Epilepsy and Depression Co-Morbidity Although a strong co-morbidity exists clinically between epilepsy and depression, the cause of this co-morbidity remains unknown, and a valid animal model is crucial for the identification of underlying mechanisms and the development of a screening tool for novel therapies. Although some rodent models of epilepsy have been reported to display behaviors relevant to affective disorders, the seizure susceptibility of animals prone to depression-like behavior has not been characterized. Toward this end, the authors assessed several forms of seizure sensitivity and epileptogenesis in rats selectively bred for vulnerability (Swim Lo-Active; SwLo) or resilience (Swim High-Active; SwHi) to depression-like phenotypes. The SwLo rats exhibit decreased motor activity in a swim test and other depression-like phenotypes, whereas the SwHi rats display increased motor activity in a swim test. SwLo rats exhibited a decreased latency to limbic motor seizures following acute pilocarpine administration in the absence of differences in pilocarpine pharmacokinetics, and also had a decreased threshold to tonic seizures induced by electroshock. Approximately half of the SwLo rats, but none of the SwHi rats, had spontaneous limbic motor seizures 5 weeks following pilocarpine-induced status epilepticus. While the number of stimulations required to achieve full amygdala and hippocampal electrical kindling were similar in the two rat lines, SwLo rats had a lower final hippocampal kindling threshold and more wet dog shakes during both amygdala and hippocampal kindling. Combined, these results indicate that SwLo rats are a model of epilepsy and depression co-morbidity that can be used for investigating underlying neurobiological and genetic mechanisms and screening novel therapeutics. Epps SA, Tabb KD, Lin SJ, Kahn AB, Javors MA, Boss-Williams KA, Weiss JM, Weinshenker D. Seizure susceptibility and epileptogenesis in a rat model of epilepsy and depression co-morbidity. Neuropsychopharmacology 2012; 37(13): 2756-2763.

Candidate Gene Studies of a Promising Intermediate Phenotype: Failure to Replicate Many candidate gene studies use 'intermediate phenotypes' instead of disease diagnoses. It has been proposed that intermediate phenotypes have simpler genetic architectures such that individual alleles account for a larger percentage of trait variance. This implies that smaller samples can be used to identify genetic associations. Pharmacogenomic drug challenge studies may be an especially promising class of intermediate phenotype. The authors previously conducted a series of 12 candidate gene analyses of acute subjective and physiological responses to amphetamine in 99-162 healthy human volunteers (ADORA2A, SLC6A3, BDNF, SLC6A4, CSNK1E, SLC6A2, DRD2, FAAH, COMT, OPRM1). Here, they report their attempt to replicate these findings in over 200 additional participants ascertained using identical methodology. They were unable to replicate any of their previous findings. These results raise critical issues related to non-replication of candidate gene studies, such as power, sample size, multiple testing within and between studies, publication bias and the expectation that true allelic effect sizes are similar to those reported in genome-wide association studies. Many of these factors may have contributed to the authors' failure to replicate their previous findings. These results should instill caution in those considering similarly designed studies. Hart AB, de Wit H, Palmer AA. Candidate gene studies of a promising intermediate phenotype: Failure to replicate. Neuropsychopharmacology 2012. Epub ahead of print.

The Role Of Histone Acetylation In Cocaine-Induced Neural Plasticity and Behavior How do drugs of abuse, such as cocaine, cause stable changes in neural plasticity that in turn drive long-term changes in behavior? What kind of mechanism can underlie such stable changes in neural plasticity? One prime candidate mechanism is epigenetic mechanisms of chromatin regulation. Chromatin regulation has been shown to generate short-term and long-term molecular memory within an individual cell. They have also been shown to underlie cell fate decisions (or cellular memory). Now, there is accumulating evidence that in the CNS, these same mechanisms may be pivotal for drug-induced changes in gene expression and ultimately long-term behavioral changes. As these mechanisms are also being found to be fundamental for learning and memory, an exciting new possibility is the extinction of drug-seeking behavior by manipulation of epigenetic mechanisms. In this review, the authors critically discuss the evidence demonstrating a key role for chromatin regulation via histone acetylation in cocaine action. Rogge GA, Wood MA. The role of histone acetylation in cocaine-induced neural plasticity and behavior. Neuropsychopharmacology 2013; 38(1): 94-110.

Molecular, Cellular, and Structural Mechanisms Of Cocaine Addiction: A Key Role For Micro RNAs The rewarding properties of cocaine play a key role in establishing and maintaining the drug-taking habit. However, as exposure to cocaine increases, drug use can transition from controlled to compulsive. Importantly, very little is known about the neurobiological mechanisms that control this switch in drug use that defines addiction. MicroRNAs (miRNAs) are small non-protein coding RNA transcripts that can regulate the expression of messenger RNAs that code for proteins. Because of their highly pleiotropic nature, each miRNA has the potential to regulate hundreds or even thousands of protein-coding RNA transcripts. This property of miRNAs has generated considerable interest in their potential involvement in complex psychiatric disorders such as addiction, as each miRNA could potentially influence the many different molecular and cellular adaptations that arise in response to drug use that are hypothesized to drive the emergence of addiction. Here, the authors review recent evidence supporting a key role for miRNAs in the ventral striatum in regulating the rewarding and reinforcing properties of cocaine in animals with limited exposure to the drug. Moreover, they discuss evidence suggesting that miRNAs in the dorsal striatum control the escalation of drug intake in rats with extended cocaine access. These findings

highlight the central role for miRNAs in drug-induced neuroplasticity in brain reward systems that drive the emergence of compulsive-like drug use in animals, and suggest that a better understanding of how miRNAs control drug intake will provide new insights into the neurobiology of drug addiction. Jonkman S, Kenny PJ. Molecular, cellular, and structural mechanisms of cocaine addiction: a key role for microRNAs. Neuropsychopharmacology 2013; 38(1): 198-211.

The Electrophysiological Signature Of Motivational Salience In Mice and Implications For Schizophrenia According to the aberrant-salience hypothesis, attribution of motivational salience is severely disrupted in patients with schizophrenia. To provide a translational approach for investigating underlying mechanisms, neural correlates of salience attribution were examined in normal mice and in a MK-801 model of schizophrenia. Electrophysiological responses to standard and deviant tones were assessed in the medial prefrontal cortex (mPFC) using an auditory oddball paradigm. Motivational salience was induced by aversive conditioning to the deviant tone. Analysis of the auditory evoked potential (AEP) showed selective modulation of the late frontal negativity (LFN) by motivational salience, which persisted throughout a 4-week delay. MK-801, an N-methyl-D-aspartic acid receptor antagonist, abolished this differential response to motivational salience in conditioned mice. In contrast, a pronounced LFN response was observed towards the deviant, ie, perceptually salient tone, in nonconditioned mice. The finding of a selective modulation of a late frontal slow wave suggests increased top-down processing and emotional evaluation of motivationally salient stimuli. In particular, the LFN is discussed as the mouse analog to the human stimulus preceding negativity, which reflects preparatory processes in anticipation of reward or punishment. MK-801 led to a disruption of the normal response in conditioned and nonconditioned mice, including an aberrantly increased LFN in nonconditioned mice. This pattern of 'false-negative' and 'false-positive' responses suggests a degradation of salience attribution, which points to mPFC responses to be relevant for translational research on cognitive alterations in schizophrenia. Moessnang C, Habel U, Schneider F, Siegel SJ. The electrophysiological signature of motivational salience in mice and implications for schizophrenia. Neuropsychopharmacology 2012; 37(13): 2846-2854.

Metabotropic Glutamate Receptor I (mGluR1) Antagonism Impairs Cocaine-Induced Conditioned Place Preference via Inhibition of Protein Synthesis Antagonism of group I metabotropic glutamate receptors (mGluR1 and mGluR5) reduces behavioral effects of drugs of abuse, including cocaine. However, the underlying mechanisms remain poorly understood. Activation of mGluR5 increases protein synthesis at synapses. Although mGluR5-induced excessive protein synthesis has been implicated in the pathology of fragile X syndrome, it remains unknown whether group I mGluR-mediated protein synthesis is involved in any behavioral effects of drugs of abuse. The authors report that group I mGluR agonist DHPG induced more pronounced initial depression of inhibitory postsynaptic currents (IPSCs) followed by modest long-term depression (I-LTD) in dopamine neurons of rat ventral tegmental area (VTA) through the activation of mGluR1. The early component of DHPG-induced depression of IPSCs was mediated by the cannabinoid CB(1) receptors, while DHPG-induced I-LTD was dependent on protein synthesis. Western blotting analysis indicates that mGluR1 was coupled to extracellular signal-regulated kinase (ERK) and mammalian target of rapamycin (mTOR) signaling pathways to increase translation. The authors also show that cocaine conditioning activated translation machinery in the VTA via an mGluR1-dependent mechanism. Furthermore, intra-VTA microinjections of mGluR1 antagonist JNJ16259685 and protein synthesis inhibitor cycloheximide significantly attenuated or blocked the acquisition of cocaine-induced conditioned place preference (CPP) and activation of translation elongation factors. Taken together, these results suggest that mGluR1 antagonism

inhibits de novo protein synthesis; this effect may block the formation of cocaine-cue associations and thus provide a mechanism for the reduction in CPP to cocaine. Neuropsychopharmacology advance online publication, 13 February 2013; doi:10.1038/npp.2013.29. Yu F. Zhong P, Liu X, Sun D, Gao HQ, Liu QS. Metabotropic glutamate receptor i (mglur1) antagonism impairs cocaine-induced conditioned place preference via inhibition of protein synthesis. Neuropsychopharmacology 2013. Epub ahead of print.

The Impact Of Gabapentin Administration On Brain GABA and Glutamate Concentrations: A 7T ^{1}H-MRS Study Gamma-aminobutyric acid (GABA) and glutamate are implicated in numerous neuropsychiatric and substance abuse conditions, but their spectral overlap with other resonances makes them a challenge to quantify in humans. Gabapentin, marketed for the treatment of seizures and neuropathic pain, has been shown to increase in vivo GABA concentration in the brain of both rodents and humans. Gabapentin effects on glutamate are not known. The authors conducted a gabapentin (900 mg) challenge in healthy human subjects to confirm and explore its effects on GABA and glutamate concentrations, respectively, and to test the ability of single voxel localized proton magnetic resonance spectroscopy (^{1}H-MRS) to reliably measure GABA and glutamate in the visual cortex at the ultra-high magnetic field of 7 Tesla. Reproducibility of GABA and glutamate measurements was determined in a comparison group without drug twice within day and 2 weeks apart. Although GABA concentration changes were small both within day (average 5.6%) and between day (average 4.8%), gabapentin administration was associated with an average increase in GABA concentration of 55.7% (6.9-91.0%). Importantly, drug-induced change in GABA levels was inversely correlated to the individual's baseline GABA level (R^2=0.72). Mean glutamate concentrations did not change significantly with or without drug administration. In conclusion, localized ^{1}H-MRS at 7 Tesla can be successfully applied to the measurement of GABA concentration and is sensitive to acute drug-induced changes in cortical GABA. Whether baseline GABA concentrations predict clinical efficacy of gabapentin is an area worthy of exploration. Cai K, Nanga RP, Lamprou L, Schinstine C, Elliott M, Hariharan H, Reddy R, Epperson CN. The impact of gabapentin administration on brain GABA and glutamate concentrations: a 7T ^{1}H-MRS study. Neuropsychopharmacology 2012; 37(13): 2764-2771.

Progress Toward Single Cell Metabolomics The metabolome refers to the entire set of small molecules, or metabolites, within a biological sample. These molecules are involved in many fundamental intracellular functions and reflect the cell's physiological condition. The ability to detect and identify metabolites and determine and monitor their amounts at the single cell level enables an exciting range of studies of biological variation and functional heterogeneity between cells, even within a presumably homogenous cell population. Significant progress has been made in the development and application of bioanalytical tools for single cell metabolomics based on mass spectrometry, microfluidics, and capillary separations. Remarkable improvements in the sensitivity, specificity, and throughput of these approaches enable investigation of multiple metabolites simultaneously in a range of individual cell samples. Rubakhin SS, Lanni EJ, Sweedler JV. Progress toward single cell metabolomics. Curr Opin Biotechnol 2013; 24(1): 95-104.

Neuroscience Of Affect: Brain Mechanisms Of Pleasure and Displeasure Affective neuroscience aims to understand how affect (pleasure or displeasure) is created by brains. Progress is aided by recognizing that affect has both objective and subjective features. Those dual aspects reflect that affective reactions are generated by neural mechanisms, selected in evolution based on their real (objective) consequences for genetic fitness. The authors review evidence for neural representation of pleasure in the brain (gained largely from neuroimaging studies), and evidence for

the causal generation of pleasure (gained largely from brain manipulation studies). They suggest that representation and causation may actually reflect somewhat separable neuropsychological functions. Representation reaches an apex in limbic regions of prefrontal cortex, especially orbitofrontal cortex, influencing decisions and affective regulation. Causation of core pleasure or 'liking' reactions is much more subcortically weighted, and sometimes surprisingly localized. Pleasure 'liking' is especially generated by restricted hedonic hotspot circuits in nucleus accumbens (NAc) and ventral pallidum. Another example of localized valence generation, beyond hedonic hotspots, is an affective keyboard mechanism in NAc for releasing intense motivations such as either positively valenced desire and/or negatively valenced dread. Berridge KC, Kringelbach ML. Neuroscience of affect: brain mechanisms of pleasure and displeasure. Curr Opin Neurobiol 2013. Epub ahead of print.

Addiction: A Drug-Induced Disorder Of Memory Reconsolidation Persistent maladaptive memories that maintain drug seeking and are resistant to extinction are a hallmark of addiction. As such, disruption of memory reconsolidation after retrieval has received attention for its therapeutic potential. Unrestrained reconsolidation may have the opposite effect, leading to reiterative and cumulative strengthening of memory over long periods of time. Here the authors review the molecular mechanisms underlying reconsolidation of appetitive and drug-rewarded memories, and discuss how these findings contribute to our understanding of the nature of this process. Finally, they suggest that drug-induced alterations to signal transduction might lead to dysregulation of reconsolidation, causing enhancements of drug-related memory after retrieval, and significantly contribute to the compulsive drug seeking that is a core component of addiction. Tronson NC, Taylor JR. Addiction: a drug-induced disorder of memory reconsolidation. Curr Opin Neurobiol 2013. Epub ahead of print.

Neural Basis Of Learning and Preference During Social Decision-Making Social decision-making is arguably the most complex cognitive function performed by the human brain. This is due to two unique features of social decision-making. First, predicting the behaviors of others is extremely difficult. Second, humans often take into consideration the well-beings of others during decision-making, but this is influenced by many contextual factors. Despite such complexity, studies on the neural basis of social decision-making have made substantial progress in the last several years. They demonstrated that the core brain areas involved in reinforcement learning and valuation, such as the ventral striatum and orbitofrontal cortex, make important contribution to social decision-making. Furthermore, the contribution of brain systems implicated for theory of mind during decision-making is being elucidated. Future studies are expected to provide additional details about the nature of information channeled through these brain areas. Seo H, Lee D. Neural basis of learning and preference during social decision-making. Curr Opin Neurobiol 2012; 22(6): 990-995.

Using Metabotropic Glutamate Receptors To Modulate Cocaine's Synaptic and Behavioral Effects: Mglur1 Finds A Niche Group I metabotropic glutamate receptors (mGluR) are important modulators of excitatory synaptic transmission and therefore potential targets for drug development. In several brain regions (ventral tegmental area (VTA), cerebellum, and amygdala), stimulation of mGluR1 selectively inhibits synaptic transmission mediated by calcium-permeable AMPA receptors (CP-AMPARs) and thus produces synaptic depression. The same relationship has now been demonstrated in the nucleus accumbens (NAc), a region that is critical for cocaine craving. CP-AMPAR levels in NAc synapses are normally low, but they increase after prolonged withdrawal from extended-access cocaine self-administration (SA). These CP-AMPARs mediate the intensified

('incubated') cue-induced cocaine craving observed under these conditions. Therefore, activation of mGluR1 with positive allosteric modulators (PAM) may reduce cue-induced relapse in abstinent cocaine addicts. Loweth JA, Tseng KY, Wolf ME. Using metabotropic glutamate receptors to modulate cocaine's synaptic and behavioral effects: mGluR1 finds a niche. Curr Opin Neurobiol 2013. Epub ahead of print.

Epigenetic Mechanisms Of Drug Addiction Epigenetic regulation can mediate long-lasting changes in gene expression, which makes it an attractive mechanism for the stable behavioral abnormalities that characterize drug addiction. Recent research has unveiled numerous types of epigenetic modifications within the brain's reward circuitry in animal models of drug addiction. In this review, the authors summarize the latest advances in the field, focusing on histone modifications, DNA methylation, and noncoding RNAs. They also highlight several areas for future research. Unraveling the highly complex epigenetic mechanisms of addiction is adding to our understanding of this syndrome and has the potential to trigger novel approaches for better diagnosis and therapy. Feng J, Nestler EJ. Epigenetic mechanisms of drug addiction. Curr Opin Neurobiol 2013. Epub ahead of print.

Pavlovian Valuation Systems In Learning And Decision Making Environmental stimuli guide value-based decision making, but can do so through cognitive representation of outcomes or through general-incentive properties attributed to the cues themselves. The authors assert that these differences are conferred through the use of alternative associative structures differing in computational intensity. Using this framework, they review scientific evidence to discern the neural substrates of these assumed separable processes. They suggest that the contribution of the mesolimbic dopamine system to Pavlovian valuation is restricted to an affective system that is only updated through experiential feedback of stimulus-outcome pairing, whereas the orbitofrontal cortex contributes to an alternative system capable of inferential reasoning. Finally they discuss the interactions and convergence of these systems and their implications for decision making and its pathology. Clark JJ, Hollon NG, Phillips PE. Pavlovian valuation systems in learning and decision making. Curr Opin Neurobiol 2012; 22(6): 1054-1061.

Analysis Of Intact Monoclonal Antibody Igg1 By Electron Transfer Dissociation Orbitrap FTMS The primary structural information of proteins employed as biotherapeutics is essential if one wishes to understand their structure-function relationship, as well as in the rational design of new therapeutics and for quality control. Given both the large size (around 150 kDa) and the structural complexity of intact immunoglobulin G (IgG), which includes a variable number of disulfide bridges, its extensive fragmentation and subsequent sequence determination by means of tandem mass spectrometry (MS) are challenging. Here, the authors applied electron transfer dissociation (ETD), implemented on a hybrid Orbitrap Fourier transform mass spectrometer (FTMS), to analyze a commercial recombinant IgG in a liquid chromatography (LC)-tandem mass spectrometry (MS/MS) top-down experiment. The lack of sensitivity typically observed during the top-down MS of large proteins was addressed by averaging time-domain transients recorded in different LC-MS/MS experiments before performing Fourier transform signal processing. The results demonstrate that an improved signal-to-noise ratio, along with the higher resolution and mass accuracy provided by Orbitrap FTMS (relative to previous applications of top-down ETD-based proteomics on IgG), is essential for comprehensive analysis. Specifically, ETD on Orbitrap FTMS produced about 33% sequence coverage of an intact IgG, signifying an almost 2-fold increase in IgG sequence coverage relative to prior ETD-based analysis of intact monoclonal antibodies of a similar subclass. These results suggest the potential application of the developed

methodology to other classes of large proteins and biomolecules. Fornelli L, Damoc E, Thomas PM, Kelleher NL, Aizikov K, Denisov E, Makarov A, Tsybin YO. Analysis of intact monoclonal antibody IgG1 by electron transfer dissociation Orbitrap FTMS. Mol Cell Proteomics 2012; 11(12): 1758-1767.

High-Definition De Novo Sequencing Of Crustacean Hyperglycemic Hormone (CHH)-Family Neuropeptides A complete understanding of the biological functions of large signaling peptides (>4 kDa) requires comprehensive characterization of their amino acid sequences and post-translational modifications, which presents significant analytical challenges. In the past decade, there has been great success with mass spectrometry-based de novo sequencing of small neuropeptides. However, these approaches are less applicable to larger neuropeptides because of the inefficient fragmentation of peptides larger than 4 kDa and their lower endogenous abundance. The conventional proteomics approach focuses on large-scale determination of protein identities via database searching, lacking the ability for in-depth elucidation of individual amino acid residues. Here, we present a multifaceted MS approach for identification and characterization of large crustacean hyperglycemic hormone (CHH)-family neuropeptides, a class of peptide hormones that play central roles in the regulation of many important physiological processes of crustaceans. Six crustacean CHH-family neuropeptides (8-9.5 kDa), including two novel peptides with extensive disulfide linkages and PTMs, were fully sequenced without reference to genomic databases. High-definition de novo sequencing was achieved by a combination of bottom-up, off-line top-down, and on-line top-down tandem MS methods. Statistical evaluation indicated that these methods provided complementary information for sequence interpretation and increased the local identification confidence of each amino acid. Further investigations by MALDI imaging MS mapped the spatial distribution and colocalization patterns of various CHH-family neuropeptides in the neuroendocrine organs, revealing that two CHH-subfamilies are involved in distinct signaling pathways. Jia C, Hui L, Cao W, Lietz CB, Jiang X, Chen R, Catherman AD, Thomas PM, Ge Y, Kelleher NL, Li L. High-definition de novo sequencing of crustacean hyperglycemic hormone (CHH)-family neuropeptides. Mol Cell Proteomics 2012; 11(12): 1951-1964.

Functional Circuits and Anatomical Distribution Of Response Properties In The Primate Amygdala Recent electrophysiological studies on the primate amygdala have advanced our understanding of how individual neurons encode information relevant to emotional processes, but it remains unclear how these neurons are functionally and anatomically organized. To address this, the authors analyzed cross-correlograms of amygdala spike trains recorded during a task in which monkeys learned to associate novel images with rewarding and aversive outcomes. Using this task, they have recently described two populations of amygdala neurons: one that responds more strongly to images predicting reward (positive value-coding), and another that responds more strongly to images predicting an aversive stimulus (negative value-coding). Here, they report that these neural populations are organized into distinct, but anatomically intermingled, appetitive and aversive functional circuits, which are dynamically modulated as animals used the images to predict outcomes. Furthermore, we report that responses to sensory stimuli are prevalent in the lateral amygdala, and are also prevalent in the medial amygdala for sensory stimuli that are emotionally significant. The circuits identified here could potentially mediate valence-specific emotional behaviors thought to involve the amygdala. Zhang W, Schneider DM, Belova MA, Morrison SE, Paton JJ, Salzman CD. Functional circuits and anatomical distribution of response properties in the primate amygdala. J Neurosci 2013; 33(2): 722-733.

Amphetamine Paradoxically Augments Exocytotic Dopamine Release and Phasic Dopamine Signals Drugs of abuse hijack brain-reward circuitry during the addiction process by augmenting action potential-dependent phasic dopamine release events associated with learning and goal-directed behavior. One prominent exception to this notion would appear to be amphetamine (AMPH) and related analogs, which are proposed instead to disrupt normal patterns of dopamine neurotransmission by depleting vesicular stores and promoting nonexocytotic dopamine efflux via reverse transport. This mechanism of AMPH action, though, is inconsistent with its therapeutic effects and addictive properties, which are thought to be reliant on phasic dopamine signaling. Here the authors used fast-scan cyclic voltammetry in freely moving rats to interrogate principal neurochemical responses to AMPH in the striatum and relate these changes to behavior. First, they showed that AMPH dose-dependently enhanced evoked dopamine responses to phasic-like current pulse trains for up to 2 h. Modeling the data revealed that AMPH inhibited dopamine uptake but also unexpectedly potentiated vesicular dopamine release. Second, they found that AMPH increased the amplitude, duration, and frequency of spontaneous dopamine transients, the naturally occurring, nonelectrically evoked, phasic increases in extracellular dopamine. Finally, using an operant sugar reward paradigm, they showed that low-dose AMPH augmented dopamine transients elicited by sugar-predictive cues. However, operant behavior failed at high-dose AMPH, which was due to phasic dopamine hyperactivity and the decoupling of dopamine transients from the reward predictive cue. These findings identify upregulation of exocytotic dopamine release as a key AMPH action in behaving animals and support a unified mechanism of abused drugs to activate phasic dopamine signaling. Daberkow DP, Brown HD, Bunner KD, Kraniotis SA, Doellman MA, Ragozzino ME, Garris PA, Roitman MF. Amphetamine paradoxically augments exocytotic dopamine release and phasic dopamine signals. J Neurosci 2013; 33(2): 452-463.

Deficits In Ventromedial Prefrontal Cortex Group 1 Metabotropic Glutamate Receptor Function Mediate Resistance To Extinction During Protracted Withdrawal From An Extensive History Of Cocaine Self-Administration Anomalies in prefrontal cortex (PFC) function are posited to underpin difficulties in learning to suppress drug-seeking behavior during abstinence. Because group 1 metabotropic glutamate receptors (mGluRs) regulate drug-related learning, the authors assayed the consequences of extended access to intravenous cocaine (6 h/d; 0.25 mg/infusion for 10 d) on the PFC expression of group 1 mGluRs and the relevance of observed changes for cocaine seeking. After protracted withdrawal, cocaine-experienced animals exhibited a time-dependent intensification of cue-induced cocaine-seeking behavior and an impaired extinction of this behavior. These behavioral phenomena were associated with a time-dependent reduction in mGluR1/5 expression within ventromedial PFC (vmPFC) of cocaine-experienced animals exposed to extinction testing but not in untested ones. Interestingly, pharmacological manipulations of vmPFC mGluR1/5 produced no immediate effects on cue-induced cocaine-seeking behavior but produced residual effects on a subsequent test for cocaine seeking. At 3 d withdrawal, cocaine-experienced rats infused intra-vmPFC with mGluR1/5 antagonists, either before or after an initial test for cocaine seeking, persisted in their cocaine seeking akin to cocaine-experienced rats in protracted withdrawal. Conversely, cocaine-experienced rats infused with an mGluR1/5 agonist before the initial test for cocaine-seeking at 30 d withdrawal exhibited a facilitation of extinction learning. These data indicate that cue-elicited deficits in vmPFC group 1 mGluR function mediate resistance to extinction during protracted withdrawal from a history of extensive cocaine self-administration and pose pharmacological stimulation of these receptors as a potential approach to facilitate learned suppression of drug-seeking behavior that may aid drug abstinence. Ben-Shahar O, Sacramento AD, Miller BW, Webb SM, Wroten MG, Silva HE, Caruana AL, Gordon EJ, Ploense KL, Ditzhazy J, Kippin TE, Szumlinski KK. Deficits in ventromedial prefrontal cortex group 1

metabotropic glutamate receptor function mediate resistance to extinction during protracted withdrawal from an extensive history of cocaine self-administration. J Neurosci 2013; 33(2): 495-506a.

Active Avoidance Learning Requires Prefrontal Suppression Of Amygdala-Mediated Defensive Reactions Signaled active avoidance (AA) paradigms train subjects to prevent an aversive outcome by performing a learned behavior during the presentation of a conditioned cue. This complex form of conditioning involves pavlovian and instrumental components, which produce competing behavioral responses that must be reconciled for the subject to successfully avoid an aversive stimulus. In signaled AA paradigm for rat, the authors tested the hypothesis that the instrumental component of AA training recruits infralimbic prefrontal cortex (ilPFC) to inhibit central amygdala (CeA)-mediated Pavlovian reactions. Pretraining lesions of ilPFC increased conditioned freezing while causing a corresponding decrease in avoidance; lesions of CeA produced opposite effects, reducing freezing and facilitating avoidance behavior. Pharmacological inactivation experiments demonstrated that ilPFC is relevant to both acquisition and expression phases of AA learning. Inactivation experiments also revealed that AA produces an ilPFC-mediated diminution of pavlovian reactions that extends beyond the training context, even when the conditioned stimulus is presented in an environment that does not allow the avoidance response. Finally, injection of a protein synthesis inhibitor into either ilPFC or CeA impaired or facilitated AA, respectively, showing that avoidance training produces two opposing memory traces in these regions. These data support a model in which AA learning recruits ilPFC to inhibit CeA-mediated defense behaviors, leading to a robust suppression of freezing that generalizes across environments. Thus, ilPFC functions as an inhibitory interface, allowing instrumental control over an aversive outcome to attenuate the expression of freezing and other reactions to conditioned threat. Moscarello JM, Ledoux JE. Active avoidance learning requires prefrontal suppression of amygdala-mediated defensive reactions. J Neurosci 2013; 33(9): 3815-3823.

Medial Prefrontal Cortex Inversely Regulates Toluene-Induced Changes In Markers Of Synaptic Plasticity Of Mesolimbic Dopamine Neurons Toluene is a volatile solvent that is intentionally inhaled by children, adolescents, and adults for its intoxicating effects. Although voluntary use of toluene suggests that it possesses rewarding properties and abuse potential, it is unknown whether toluene alters excitatory synaptic transmission in reward-sensitive dopamine neurons like other drugs of abuse. Here, using a combination of retrograde labeling and slice electrophysiology, the authors show that a brief in vivo exposure of rats to a behaviorally relevant concentration of toluene vapor enhances glutamatergic synaptic strength of dopamine (DA) neurons projecting to nucleus accumbens core and medial shell neurons. This effect persisted for up to 3 d in mesoaccumbens core DA neurons and for at least 21 d in those projecting to the medial shell. In contrast, toluene vapor exposure had no effect on synaptic strength of DA neurons that project to the medial prefrontal cortex (mPFC). Furthermore, infusion of GABAergic modulators into the mPFC before vapor exposure to pharmacologically manipulate output, inhibited, or potentiated toluene's action on mesoaccumbens DA neurons. Together, the results of these studies indicate that toluene induces a target-selective increase in mesolimbic DA neuron synaptic transmission and strongly implicates the mPFC as an important regulator of drug-induced plasticity of mesolimbic dopamine neurons. Beckley JT, Evins CE, Fedarovich H, Gilstrap MJ, Woodward JJ. Medial prefrontal cortex inversely regulates toluene-induced changes in markers of synaptic plasticity of mesolimbic dopamine neurons. J Neurosci 2013; 33(2): 804-813.

Stress Produces Aversion and Potentiates Cocaine Reward By Releasing Endogenous Dynorphins In The Ventral Striatum To Locally Stimulate Serotonin Reuptake Activation of the dynorphin/κ-opioid receptor (KOR) system by repeated stress exposure or agonist treatment produces place aversion, social avoidance, and reinstatement of extinguished cocaine place preference behaviors by stimulation of p38α MAPK, which subsequently causes the translocation of the serotonin transporter (SERT, SLC6A4) to the synaptic terminals of serotonergic neurons. In the present study the authors extend those findings by showing that stress-induced potentiation of cocaine conditioned place preference occurred by a similar mechanism. In addition, SERT knock-out mice did not show KOR-mediated aversion, and selective reexpression of SERT by lentiviral injection into the dorsal raphe restored the prodepressive effects of KOR activation. Kinetic analysis of several neurotransporters demonstrated that repeated swim stress exposure selectively increased the V(max) but not K(m) of SERT without affecting dopamine transport or the high-capacity, low-affinity transporters. Although the serotonergic neurons in the dorsal raphe project throughout the forebrain, a significant stress-induced increase in cell-surface SERT expression was only evident in the ventral striatum, and not in the dorsal striatum, hippocampus, prefrontal cortex, amygdala, or dorsal raphe. Stereotaxic microinjections of the long-lasting KOR antagonist norbinaltorphimine demonstrated that local KOR activation in the nucleus accumbens, but not dorsal raphe, mediated this stress-induced increase in ventral striatal surface SERT expression. Together, these results support the hypothesis that stress-induced activation of the dynorphin/KOR system produces a transient increase in serotonin transport locally in the ventral striatum that may underlie some of the adverse consequences of stress exposure, including the potentiation of the rewarding effects of cocaine. Schindler AG, Messinger DI, Smith JS, Shankar H, Gustin RM, Schattauer SS, Lemos JC, Chavkin NW, Hagan CE, Neumaier JF, Chavkin C. Stress produces aversion and potentiates cocaine reward by releasing endogenous dynorphins in the ventral striatum to locally stimulate serotonin reuptake. J Neurosci 2012; 32(49): 17582-17596.

BEHAVIORAL AND BRAIN DEVELOPMENT RESEARCH

Regional Brain Morphometry and Impulsivity in Adolescents Following Prenatal Exposure to Cocaine and Tobacco Animal studies have suggested that prenatal cocaine exposure (PCE) deleteriously influences the developing nervous system, in part attributable to its site of action in blocking the function of monoamine reuptake transporters, increasing synaptic levels of serotonin and dopamine. The objective of this study was to examine the brain morphologic features and associated impulsive behaviors in adolescents following prenatal exposure to cocaine and/or tobacco. Magnetic resonance imaging data and behavioral measures were collected from adolescents followed up longitudinally in the Maternal Lifestyle Study. The study setting was a hospital-based research center. A total of 40 adolescent participants aged 13 to 15 years were recruited, 20 without PCE and 20 with PCE; a subset of each group additionally had tobacco exposure. Participants were selected and matched based on head circumference at birth, gestational age, maternal alcohol use, age, sex, race/ethnicity, IQ, family poverty, and socioeconomic status. Outcome measures included subcortical volumetric measures of the thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and nucleus accumbens; cortical thickness measures of the dorsolateral prefrontal cortex and ventral medial prefrontal cortex; and impulsivity assessed by Conners' Continuous Performance Test and the Sensation Seeking Scale for Children. After controlling for covariates, cortical thickness of the right dorsolateral prefrontal cortex was significantly thinner in adolescents following PCE (P = .03), whereas the pallidum volume was smaller in adolescents following prenatal tobacco exposure (P = .03). Impulsivity was correlated with thalamic volume following either PCE (P = .05) or prenatal tobacco exposure (P = .04). Prenatal cocaine or tobacco exposure can differentially affect structural brain maturation during adolescence and underlie enhanced susceptibility to impulsivity. Additional studies with larger sample sizes are warranted. Liu J, Lester BM, Neyzi N, Sheinkopf SJ, Gracia L, Kekatpure M, Kosofsky BE. Regional brain morphometry and impulsivity in adolescents following prenatal exposure to cocaine and tobacco. JAMA Pediatr. 2013 Feb 11:1-7.

Prenatal Methamphetamine Exposure, Home Environment, and Primary Caregiver Risk Factors Predict Child Behavioral Problems at 5 Years This study investigated the prospective association between prenatal methamphetamine (MA) exposure and child behavioral problems at 5 years while also examining the home environment at 30 months and several primary caregiver (PC) risk factors. Participants were 97 MA-exposed and 117 comparison children and their PCs enrolled in the Infant Development, Environment and Lifestyle Study. Hypotheses were that child behaviors would be adversely impacted by (a) prenatal MA exposure, (b) home environments that provided less developmental stimulation and emotional responsiveness to the child, and (c) the presence of PC psychological symptoms and other risk factors. Prenatal MA exposure was associated with child externalizing behavioral problems at 5 years. Home environments that were more conducive to meeting children's developmental and emotional needs were associated with fewer internalizing and externalizing behavioral problems. Independent of prenatal MA exposure, PC parenting stress and psychological symptoms were associated with increased child behavioral problems. Findings suggest prenatal MA exposure may contribute to externalizing behavioral problems in early childhood and the importance of considering possible vulnerabilities related to prenatal MA exposure in the context of the child's caregiving environment. Twomey J, LaGasse L, Derauf C, Newman E, Shah R, Smith L, Arria A, Huestis M, DellaGrotta S, Roberts M, Dansereau L, Neal C, Lester B. Prenatal methamphetamine exposure, home environment, and primary caregiver risk factors predict child behavioral problems at 5 years. Am J Orthopsychiatry. 2013 Jan; 83(1): 64-72.

Cortisol Reactivity in Two-Year-Old Children Prenatally Exposed to Methamphetamine
Until now, the functioning of the hypothalamic-pituitary-adrenal (HPA) axis in children with prenatal methamphetamine exposure (PME) had been unexamined. Previous research indicates that prenatal exposure to stimulant drugs is associated with dose-response alterations in neural growth and connectivity and consequent neurobehavioral deficits. In addition, children of drug-using parents are at an increased risk for exposure to chronic postnatal stress. In this preliminary study, the authors examined the associations of PME and postnatal environmental stress with cortisol stress reactivity in children with PME. Participants were 2-year-old children (N = 123; 55.3% male) with PME from a multicenter longitudinal Infant, Development, Environment, and Lifestyle Study. Saliva samples were obtained before and after a stress-inducing separation task. Hierarchical multiple regression analyses examined prenatal drug exposure, methodological and postnatal stress covariates, and interactions between levels of PME and postnatal stress. Mild to moderate potential for child physical abuse moderated increased cortisol reactivity in high exposed children with PME. Blunted cortisol reactivity was associated with caregiver's postnatal alcohol use, child's behavioral dysregulation, and the interaction between higher levels of PME and caregiver's psychopathology. Consistent with the known effects of stimulant drugs and chronically stressful environments on the HPA axis and, thus, the toxic stress and allostatic load phenomena, our results imply that elevated PME may be associated with alterations in the programming of the HPA axis reflecting hyperactivity, which under significant and chronic environmental stress then may become hypoactive. Kirlic N, Newman E, Lagasse LL, Derauf C, Shah R, Smith LM, Arria AM, Huestis MA, Haning W, Strauss A, Dellagrotta S, Dansereau LM, Abar B, Neal CR, Lester BM. Cortisol reactivity in two-year-old children prenatally exposed to methamphetamine. J Stud Alcohol Drugs. 2013 May; 74(3): 447-451.

Adolescent Initiation of Drug Use: Effects of Prenatal Cocaine Exposure The purpose of this study was to investigate the direct effects of prenatal cocaine exposure (PCE) on adolescent drug use, while controlling for other predictors of adolescent use. Data are from a longitudinal study of PCE in which women and their offspring were assessed throughout childhood. Adolescents were interviewed at 15 years about their age at initiation of alcohol, marijuana, and tobacco. The sample consisted of 214 adolescents and their caregivers: 50% was of white ethnicity, and 50% African American. First trimester cocaine exposure significantly predicted earlier adolescent marijuana and alcohol initiation. The hazard of marijuana and alcohol initiation among exposed adolescents was almost two times greater than among nonexposed adolescents, adjusting for other significant factors. There were no differences in tobacco initiation. Other significant predictors of adolescent drug use were family history of alcohol problems, exposure to violence, and childhood maltreatment. Cocaine exposure during early pregnancy was associated with initiation of marijuana and alcohol use. Exposure to violence, childhood maltreatment, and familial factors also predicted adolescent initiation, but did not mitigate the effects of PCE. The combination of these risk factors has significant implications for the development of later substance use, social, and psychiatric problems. Richardson GA, Larkby C, Goldschmidt L, Day NL. Adolescent initiation of drug use: effects of prenatal cocaine exposure. J Am Acad Child Adolesc Psychiatry. 2013 Jan; 52(1): 37-46.

The Effect of Prenatal Methamphetamine Exposure on Attention as Assessed by Continuous Performance Tests: Results From the Infant Development, Environment, and Lifestyle Study
The investigators of this study assessed the increased risk of attention-deficit hyperactivity disorder (ADHD) in young children with prenatal methamphetamine exposure from the multicenter, longitudinal Infant Development, Environment, and Lifestyle (IDEAL) study. The IDEAL study enrolled 412 mother-infant pairs at 4 sites (Tulsa, OK; Des Moines, IA; Los Angeles, CA; and

Honolulu, HI). Methamphetamine-exposed subjects (n = 204) were identified by self-report and/or gas chromatography/mass spectrometry confirmation of amphetamine and metabolites in infant meconium. Matched subjects (n = 208) denied methamphetamine use and had a negative meconium screen. This analysis included a subsample of 301 subjects who were administered the Conners' Kiddie Continuous Performance Test (K-CPT) at 5.5 years of age (153 exposed and 148 comparison). Hierarchical linear models adjusted for covariates tested exposure effects on K-CPT measures. Using the same covariates, logistic regression was used to determine the effect of exposure on the incidence of a positive ADHD confidence index score, defined as greater than 50%. There were no differences between the groups in omission or commission errors or reaction time for correct trials. However, methamphetamine exposure was associated with subtle differences in other outcomes predictive of ADHD, including increased slope of reaction time across blocks ($p < .001$), increased variability in reaction time with longer interstimulus intervals ($p < .01$), and increased likelihood of greater than 50% on the ADHD confidence index (odds ratio, 3.1; 95% confidence interval, 1.2-7.8; $p = .02$). Prenatal methamphetamine exposure was associated with subtle differences in K-CPT scores at 5.5 years of age. Even at this relatively young age, these children exhibit indicators of risk for ADHD and warrant monitoring. Kiblawi ZN, Smith LM, LaGasse LL, Derauf C, Newman E, Shah R, Arria A, Huestis M, DellaGrotta S, Dansereau LM, Neal C, Lester B. The effect of prenatal methamphetamine exposure on attention as assessed by continuous performance tests: results from the Infant Development, Environment, and Lifestyle study. J Dev Behav Pediatr. 2013 Jan; 34(1): 31-37.

Perceived Child Behavior Problems, Parenting Stress, and Maternal Depressive Symptoms Among Prenatal Methamphetamine Users The present study was designed to examine parenting stress, maternal depressive symptoms, and perceived child behavior problems among mothers who used methamphetamine (MA) during pregnancy. Participants were a subsample (n = 212; 75 exposed, 137 comparison) of biological mothers who had continuous custody of their child from birth to 36 months. The subsample was drawn from a larger, ongoing longitudinal study on the effects of prenatal methamphetamine exposure (n = 412; 204 exposed, 208 comparison). Mothers who used MA during pregnancy reported more parenting stress and more depressive symptoms than a matched comparison group. There were no differences between groups on perceived child behavior problems. In a hierarchical linear model, depressive symptoms, and perceived child behavior problems, but not MA exposure, were statistically significant predictors of parenting stress. Screening for potential parenting problems among mothers with a history of substance abuse is warranted. Parenting interventions targeting depressive symptoms, parenting stress, and child behavior problems are needed for this population. Liles BD, Newman E, Lagasse LL, Derauf C, Shah R, Smith LM, Arria AM, Huestis MA, Haning W, Strauss A, Dellagrotta S, Dansereau LM, Neal C, Lester BM. Perceived child behavior problems, parenting stress, and maternal depressive symptoms among prenatal methamphetamine users. Child Psychiatry Hum Dev. 2012 Dec; 43(6): 943-957.

Multimodal Imaging of the Self-regulating Developing Brain Self-regulation refers to the ability to control behavior, cognition, and emotions, and self-regulation failure is related to a range of neuropsychiatric problems. It is poorly understood how structural maturation of the brain brings about the gradual improvement in self-regulation during childhood. In a large-scale multicenter effort, 735 children (4-21 y) underwent structural MRI for quantification of cortical thickness and surface area and diffusion tensor imaging for quantification of the quality of major fiber connections. Brain development was related to a standardized measure of cognitive control (the flanker task from the National Institutes of Health Toolbox), a critical component of self-regulation.

Ability to inhibit responses and impose cognitive control increased rapidly during preteen years. Surface area of the anterior cingulate cortex accounted for a significant proportion of the variance in cognitive performance. This finding is intriguing, because characteristics of the anterior cingulum are shown to be related to impulse, attention, and executive problems in neurodevelopmental disorders, indicating a neural foundation for self-regulation abilities along a continuum from normality to pathology. The relationship was strongest in the younger children. Properties of large-fiber connections added to the picture by explaining additional variance in cognitive control. Although cognitive control was related to surface area of the anterior cingulate independently of basic processes of mental speed, the relationship between white matter quality and cognitive control could be fully accounted for by speed. The results underscore the need for integration of different aspects of brain maturation to understand the foundations of cognitive development. Fjell AM, Walhovd KB, Brown TT, Kuperman JM, Chung Y, Hagler DJ Jr, Venkatraman V, Roddey JC, Erhart M, McCabe C, Akshoomoff N, Amaral DG, Bloss CS, Libiger O, Darst BF, Schork NJ, Casey BJ, Chang L, Ernst TM, Gruen JR, Kaufmann WE, Kenet T, Frazier J, Murray SS, Sowell ER, van Zijl P, Mostofsky S, Jernigan TL, Dale AM; Pediatric Imaging, Neurocognition, and Genetics Study. Multimodal imaging of the self-regulating developing brain. Proc Natl Acad Sci U S A. 2012 Nov 27; 109(48): 19620-19625.

Intergenerational Transmission of Risk for Social Inhibition: The Interplay Between Parental Responsiveness and Genetic Influences To better understand mechanisms underlying the intergenerational transmission of social anxiety, the authors used a prospective adoption design to examine the roles of genetic influences (inferred from birth mothers' social phobia) and rearing environment (adoptive mothers' and fathers' responsiveness) on the development of socially inhibited, anxious behaviors in children between 18 and 27 months of age. The sample consisted of 275 adoption-linked families, each including an adopted child, adoptive parents, and a birth mother. Results indicated that children whose birth mothers met criteria for the diagnosis of social phobia showed elevated levels of observed behavioral inhibition in a social situation at 27 months of age if their adoptive mothers provided less emotionally and verbally responsive rearing environments at 18 months of age. Conversely, in the context of higher levels of maternal responsiveness, children of birth mothers with a history of social phobia did not show elevated levels of behavioral inhibition. These findings on maternal responsiveness were replicated in a model predicting parent reports of child social anxiety. The findings are discussed in terms of gene-environment interactions in the intergenerational transmission of social anxiety. Natsuaki MN, Leve LD, Neiderhiser JM, Shaw DS, Scaramella LV, Ge X, Reiss D. Intergenerational transmission of risk for social inhibition: The interplay between parental responsiveness and genetic influences. Dev Psychopathol. 2013 Feb; 25(1): 261-274.

Opioid Receptor Polymorphism A118G Associated with Clinical Severity in a Drug Overdose Population Genetic variations in the human mu-opioid receptor gene (OPRM1) mediate individual differences in response to pain and opiate addiction. The authors studied whether the common A118G (rs1799971) mu-opioid receptor single nucleotide polymorphism (SNP) was associated with overdose severity in humans. In addition, they examined an SNP responsible for alternative splicing of OPRM1 (rs2075572). They assessed allele frequencies of the above SNPs and associations with clinical severity in patients presenting to the emergency department (ED) with acute drug overdose. This work was designed as an observational cohort study over a 12-month period at an urban teaching hospital. Participants consisted of consecutive adult ED patients with suspected acute drug overdose for whom discarded blood samples were available for analysis. Specimens were linked with clinical variables (demographics, urine toxicology screens, clinical outcomes) then deidentified

prior to genetic SNP analysis. Blinded genotyping was performed after standard DNA purification and whole genome amplification. In-hospital severe outcomes were defined as either respiratory arrest (RA; defined by mechanical ventilation) or cardiac arrest (CA; defined by loss of pulse). The authors analyzed 179 patients (61% male, median age 32) who overall suffered 15 RAs and four CAs, of whom three died. The 118G allele conferred 5.3-fold increased odds of CA/RA ($p<0.05$), while the rs2075572 variant allele was not associated with CA/RA. The 118G variant allele in the OPRM1 gene is associated with worse clinical severity in patients with acute drug overdose. These findings mark the first time that the 118G variant allele is linked with clinical drug overdose vulnerability. Manini AF, Jacobs MM, Vlahov D, Hurd YL. Opioid receptor polymorphism a118g associated with clinical severity in a drug overdose population. J Med Toxicol. 2013 Jan 15. [Epub ahead of print].

Longitudinal Changes in White Matter Integrity among Adolescent Substance Users The influence of repeated substance use during adolescent neurodevelopment remains unclear as there have been few prospective investigations. The aims of this study were to identify longitudinal changes in fiber tract integrity associated with alcohol- and marijuana-use severity over the course of 1.5 years. Adolescents with extensive marijuana- and alcohol-use histories by mid-adolescence ($n = 41$) and youth with consistently minimal if any substance use ($n = 51$) were followed over 18 months. Teens received diffusion tensor imaging and detailed substance-use assessments with toxicology screening at baseline and 18-month follow-ups (i.e., 182 scans in all), as well as interim substance-use interviews each 6 months. At an 18-month follow-up, substance users showed poorer white matter integrity in 7 tracts: (i) right superior longitudinal fasciculus, (ii) left superior longitudinal fasciculus, (iii) right posterior thalamic radiations, (iv) right prefrontal thalamic fibers, (v) right superior temporal gyrus white matter, (vi) right inferior longitudinal fasciculus, and (vii) left posterior corona radiata ($ps < 0.01$). More alcohol use during the interscan interval predicted higher mean diffusivity (i.e., worsened integrity) in right ($p < 0.05$) and left ($p = 0.06$) superior longitudinal fasciculi, above and beyond baseline values in these bundles. Marijuana use during the interscan interval did not predict change over time. More externalizing behaviors at Time 1 predicted lower fractional anisotropy and higher radial diffusivity (i.e., poorer integrity) of the right prefrontal thalamic fibers ($p < 0.025$). Findings add to previous cross-sectional studies reporting white matter disadvantages in youth with substance-use histories. In particular, alcohol use during adolescent neurodevelopment may be linked to reductions in white matter quality in association fiber tracts with frontal connections. In contrast, youth who engage in a variety of risk-taking behaviors may have unique neurodevelopmental trajectories characterized by truncated development in fronto-thalamic tracts, which could have functional and clinical consequences in young adulthood. Bava S, Jacobus J, Thayer RE, Tapert SF. Longitudinal changes in white matter integrity among adolescent substance users. Alcohol Clin Exp Res. 2013 Jan; 37 Suppl 1:E181-189.

Lower Glial Metabolite Levels in Brains of Young Children with Prenatal Nicotine Exposure Many pregnant women smoke cigarettes during pregnancy, but the effect of nicotine on the developing human brain is not well understood, especially in young children. This study aims to determine the effects of prenatal nicotine exposure (PNE) on brain metabolite levels in young (3-4 years old) children, using proton magnetic resonance spectroscopy ((1)H MRS). Twenty-six children with PNE and 24 nicotine-unexposed children (controls) were evaluated with a structured examination, a battery of neuropsychological tests, and MRI/(1)H MRS (without sedation). Concentrations of N-acetyl compounds (NA), total creatine (tCR), choline-containing compounds (CHO), myo-inositol (MI), and glutamate+glutamine (GLX) were measured in four brain regions. Children with PNE had similar performance to controls on neuropsychological testing. However,

compared to controls, the PNE group had lower MI (repeated measures ANOVA-p = 0.03) and tCr levels (repeated measures ANOVA-p = 0.003), especially in the basal ganglia of the girls (-19.3%, p = 0.01). In contrast, GLX was elevated in the anterior cingulate cortex of the PNE children (+9.4%, p = 0.03), and those with the highest GLX levels had the poorest performance on vocabulary (r = -0.67; p < 0.001) and visual motor integration (r = -0.53; p = 0.01). The amount of prenatal nicotine exposure did not correlate with metabolite concentrations. These findings suggest that PNE may lead to subclinical abnormalities in glial development, especially in the basal ganglia, and regionally specific changes in other neurometabolites. These alterations were not influenced by the amount of nicotine exposure prenatally. However, the effects of PNE on energy metabolism may be sex specific, with greater alterations in girls. Chang L, Cloak CC, Jiang CS, Hoo A, Hernandez AB, Ernst TM. Lower glial metabolite levels in brains of young children with prenatal nicotine exposure. J Neuroimmune Pharmacol. 2012 Mar; 7(1): 243-252.

The Context of Desire to use Marijuana: Momentary Assessment of Young People Who Frequently Use Marijuana Drawing on factors identified in the literature, this study explored in-the-moment associations of social, emotional, and temporal contexts and perceived marijuana availability with desire to use the drug, using momentary sampling methodology with young people who frequently use marijuana. Forty-one adolescent/young adult medical outpatients aged 15 to 24 years who reported using marijuana at least twice a week completed 2,912 brief questionnaires on a handheld computer in response to signals emitted at random four to six times a day for 2 weeks. The questionnaires assessed, for the moment when signaled, desire to use marijuana, location, companionship, perceived ease of getting marijuana (availability), positive affect, and negative affect. Participants reported any desire to use marijuana on 1,528 reports (55%). Companionship, perceived availability, and positive affect were independently associated with having any desire to use marijuana. Once desire to use marijuana was present, time of day, positive affect, and negative affect were independently associated with strength of desire. By collecting data in real time, in real life, this study highlights the importance of examining and intervening on emotional, environmental, and temporal contexts for youth who frequently use marijuana in order to reduce their desire to use the drug. Shrier LA, Walls CE, Kendall AD, Blood EA. The context of desire to use marijuana: momentary assessment of young people who frequently use marijuana. Psychol Addict Behav. 2012 Dec; 26(4): 821-829.

Individual and Contextual Predictors of Severity of Marijuana Use Events among Young Frequent Users This study used momentary sampling to characterize marijuana events among young frequent users and determine contextual and individual predictors of use severity. Medical clinic outpatients aged 15-24 who used marijuana at least twice a week completed a baseline assessment, then used a handheld computer to report marijuana use at 4-6 signal-prompted times per day and before/after use for 2 weeks. Reports assessed event characteristics (when, with whom, where, how, why, how much, how high). Timestamps identified time, weekend, and duration for each event. Generalized estimating equations tested associations of individual and event-specific contextual characteristics with hits/event, duration, and high. Forty-one youth completed 3868 momentary reports; 40 (98%) reported at least one marijuana use event (N=432 events; M=10.5/participant) and thus provided data for these analyses. Marijuana was most commonly used with other people (74% of events), at home (58%), via blunt (66%), and for social or enhancement reasons (86%). Most events (62%) occurred on weekdays; use was least likely in the morning (8%). Most events involved 6 or more hits (81%). Mean high was 5.2 (out of 8). Of events with start and end times (n=250), mean duration was 46.8 min. Poor mental health and use with a blunt or a bong, in the morning or evening, and on the weekend were associated with 6 or more hits/event. Female

gender was associated with greater event duration. Poor mental health predicted higher high. Among youth who used it frequently, marijuana was used in a variety of contexts, with diversity in method, dose, and duration. Contextual factors appeared to predict marijuana dose for a given event, while individual characteristics were more predictive of high and duration. Shrier LA, Walls C, Rhoads A, Blood EA. Individual and contextual predictors of severity of marijuana use events among young frequent users. Addict Behav. 2013 Jan; 38(1): 1448-1456.

Protective Factors Can Mitigate Behavior Problems after Prenatal Cocaine and Other Drug Exposures The authors determined the role of risk and protective factors on the trajectories of behavior problems associated with high prenatal cocaine exposure (PCE)/polydrug exposure. The Maternal Lifestyle Study enrolled 1,388 children with or without PCE, assessed through age 15 years. Because most women using cocaine during pregnancy also used other substances, the authors analyzed for the effects of 4 categories of prenatal drug exposure: high PCE/other drugs (OD), some PCE/OD, OD/no PCE, and no PCE/no OD. Risks and protective factors at individual, family, and community levels that may be associated with behavior outcomes were entered stepwise into latent growth curve models, then replaced by cumulative risk and protective indexes, and finally by a combination of levels of risk and protective indexes. Main outcome measures were the trajectories of externalizing, internalizing, total behavior, and attention problems scores from the Child Behavior Checklist (parent). A total of 1022 (73.6%) children had known outcomes. High PCE/OD significantly predicted externalizing, total, and attention problems when considering the balance between risk and protective indexes. Some PCE/OD predicted externalizing and attention problems. OD/no PCE also predicted behavior outcomes except for internalizing behavior. High level of protective factors was associated with declining trajectories of problem behavior scores over time, independent of drug exposure and risk index scores. High PCE/OD is a significant risk for behavior problems in adolescence; protective factors may attenuate its detrimental effects. Clinical practice and public health policies should consider enhancing protective factors while minimizing risks to improve outcomes of drug-exposed children. Bada HS, Bann CM, Whitaker TM, Bauer CR, Shankaran S, Lagasse L, Lester BM, Hammond J, Higgins R. Protective factors can mitigate behavior problems after prenatal cocaine and other drug exposures. Pediatrics. 2012 Dec; 130(6): 1479-1488.

Adolescents' fMRI Activation to a Response Inhibition Task Predicts Future Substance Use Deficient behavioral regulation may be a risk factor for substance use disorders in adolescents. Abnormalities in brain regions critical to cognitive control have been linked to more intense and problematic future substance use (e.g., Durazzo, Gazdzinski, Mon, & Meyerhoff, 2010; Falk, Berkman, Whalen, & Lieberman, 2011; Paulus, Tapert, & Schuckit, 2005). The goal of this study was to examine the degree to which brain response to an inhibition task measured in mid-adolescence can predict substance use 18 months later. Adolescents aged 16-19 (N=80) performed a go/no-go response inhibition task during fMRI at project baseline, and were followed 18 months later with a detailed interview on substance use and dependence symptoms. Participants were 39 high frequency users and 41 demographically similar low frequency users (458 versus 2 average lifetime drug use occasions at baseline, respectively). Across all subjects, no-go trials produced significant increases in neural response in the ventromedial prefrontal cortex and a region including the left angular and supramarginal gyri ($p(FWE)<.01$, cluster threshold ≥ 30 voxels). Less ventromedial prefrontal activation but more left angular gyrus activation predicted higher levels of substance use and dependence symptoms in the following 18 months, particularly for those who were high frequency users in mid-adolescence ($p<.05$). These findings are consistent with studies showing that impairments in cognitive control have strong associations with substance use. The

authors found a predictive relationship between atypical activation patterns at baseline and substance use behavior 18 months later, particularly among adolescents with histories of previous heavy use. Mahmood OM, Goldenberg D, Thayer R, Migliorini R, Simmons AN, Tapert SF. Adolescents' fMRI activation to a response inhibition task predicts future substance use. Addict Behav. 2013 Jan; 38(1): 1435-1441.

The Minnesota Center for Twin and Family Research Genome-Wide Association Study As part of the Genes, Environment and Development Initiative, the Minnesota Center for Twin and Family Research (MCTFR) undertook a genome-wide association study, which the authors describe here. A total of 8,405 research participants, clustered in four-member families, have been successfully genotyped on 527,829 single nucleotide polymorphism (SNP) markers using lllumina's Human660W-Ouad array. Quality control screening of samples and markers as well as SNP imputation procedures are described. We also describe methods for ancestry control and how the familial clustering of the MCTFR sample can be accounted for in the analysis using a Rapid Feasible Generalized Least Squares algorithm. The rich longitudinal MCTFR assessments provide numerous opportunities for collaboration. Miller MB, Basu S, Cunningham J, Eskin E, Malone SM, Oetting WS, Schork N, Sul JH, Iacono WG, McGue M. The Minnesota Center for Twin and Family Research genome-wide association study. Twin Res Hum Genet. 2012 Dec; 15(6): 767-774.

Gene-Environment Correlation in the Development of Adolescent Substance Abuse: Selection Effects of Child Personality and Mediation via Contextual Risk Factors The authors used a longitudinal twin design to examine selection effects of personality traits at age 11 on high-risk environmental contexts at age 14 and the extent to which these contexts mediated risk for substance abuse at age 17. Socialization at age 11 (willingness to follow rules and endorse conventional values) predicted exposure to contextual risk at age 14. Contextual risk partially mediated the effect of socialization on substance abuse, though socialization also had a direct effect. In contrast, boldness at age 11 (social engagement and assurance, thrill seeking, and stress resilience) also predicted substance abuse directly but was unrelated to contextual risk. There was substantial overlap in the genetic and shared environmental influences on socialization and contextual risk, and genetic risk in socialization contributed to substance abuse indirectly via increased exposure to contextual risk. This suggests that active gene-environment correlations related to individual differences in socialization contributed to an early, high-risk developmental trajectory for adolescent substance abuse. In contrast, boldness appeared to index an independent and direct genetic risk factor for adolescent substance abuse. Hicks BM, Johnson W, Durbin CE, Blonigen DM, Iacono WG, McGue M. Gene-environment correlation in the development of adolescent substance abuse: Selection effects of child personality and mediation via contextual risk factors. Dev Psychopathol. 2013 Feb; 25(1): 119-132.

Three Mutually Informative Ways to Understand the Genetic Relationships among Behavioral Disinhibition, Alcohol Use, Drug Use, Nicotine Use/Dependence, and Their Co-occurrence: Twin Biometry, GCTA, and Genome-Wide Scoring Behavioral disinhibition is a trait hypothesized to represent a general vulnerability to the development of substance use disorders. The authors used a large community-representative sample (N = 7,188) to investigate the genetic and environmental relationships among measures of behavioral disinhibition, Nicotine Use/Dependence, Alcohol Consumption, Alcohol Dependence, and Drug Use. First, using a subsample of twins (N = 2,877), they used standard twin models to estimate the additive genetic, shared environmental, and non-shared environmental contributions to these five traits. Heritabilities ranged from .42 to .58 and shared environmental effects ranged from .12 to .24. Phenotypic

correlations among the five traits were largely attributable to shared genetic effects. Second, they used Genome-wide Complex Trait Analysis (GCTA) to estimate as a random effect the aggregate genetic effect attributable to 515,384 common SNPs. The aggregated SNPs explained 10-30 % of the variance in the traits. Third, a genome-wide scoring approach summed the actual SNPs, creating a SNP-based genetic risk score for each individual. After tenfold internal cross-validation, the SNP sum score correlated with the traits at .03 to .07 ($p < .05$), indicating small but detectable effects. SNP sum scores generated on one trait correlated at approximately the same magnitude with other traits, indicating detectable pleiotropic effects among these traits. Behavioral disinhibition thus shares genetic etiology with measures of substance use, and this relationship is detectable at the level of measured genomic variation. Vrieze SI, McGue M, Miller MB, Hicks BM, Iacono WG. Three mutually informative ways to understand the genetic relationships among behavioral disinhibition, alcohol use, drug use, nicotine use/dependence, and their co-occurrence: twin biometry, gcta, and genome-wide scoring. Behav Genet. 2013 Mar; 43(2): 97-107.

Maternal Oxytocin Response during Mother-Infant Interaction: Associations with Adult Temperament Oxytocin is a neuropeptide associated with social affiliation and maternal caregiving. However, its effects appear to be moderated by various contextual factors and stable individual characteristics. The purpose of this study was to investigate the relationship of self-reported state and trait measures (such as temperament, mood and affect) with peripheral oxytocin response in mothers. Fifty-five first-time mothers participated in a semi-structured procedure, during which time repeated peripheral oxytocin levels were measured before, during and after an episode of mother-infant interaction. The maternal oxytocin response was then calculated, based on the difference in oxytocin concentration between initial baseline and interaction phase. Mothers also completed state measures of positive and negative affect and depression, and trait measures of temperament, personality disturbance and depression across time. Regression analyses determined which factors were independently associated with maternal oxytocin response. The trait measure of adult temperament emerged as a significant predictor of oxytocin response. Two out of four Adult Temperament Questionnaire factor scales were independently associated with oxytocin response: Effortful Control was negatively associated, whereas Orienting Sensitivity was positively associated. No state measure significantly predicted oxytocin response. The results indicate that mothers who show an increased oxytocin response when interacting with their infants are more sensitive of moods, emotions and physical sensations; and less compulsive, schedule driven and task oriented. These findings link differences in individual temperament in new mothers with the peripheral oxytocin response, which may have implications in the pharmacologic treatment of disorders such as maternal neglect, post-partum depression and maternal addiction. This article is part of a Special Issue entitled Oxytocin, Vasopressin, and Social Behavior. Strathearn L, Iyengar U, Fonagy P, Kim S. Maternal oxytocin response during mother-infant interaction: associations with adult temperament. Horm Behav. 2012 Mar; 61(3): 429-435.

Long-Term Influence of Normal Variation in Neonatal Characteristics on Human Brain Development It is now recognized that a number of cognitive, behavioral, and mental health outcomes across the lifespan can be traced to fetal development. Although the direct mediation is unknown, the substantial variance in fetal growth, most commonly indexed by birth weight, may affect lifespan brain development. The authors investigated effects of normal variance in birth weight on MRI-derived measures of brain development in 628 healthy children, adolescents, and young adults in the large-scale multicenter Pediatric Imaging, Neurocognition, and Genetics study. This heterogeneous sample was recruited through geographically dispersed sites in the United States. The influence of birth weight on cortical thickness, surface area, and striatal and total brain

volumes was investigated, controlling for variance in age, sex, household income, and genetic ancestry factors. Birth weight was found to exert robust positive effects on regional cortical surface area in multiple regions as well as total brain and caudate volumes. These effects were continuous across birth weight ranges and ages and were not confined to subsets of the sample. The findings show that (i) aspects of later child and adolescent brain development are influenced at birth and (ii) relatively small differences in birth weight across groups and conditions typically compared in neuropsychiatric research (e.g., Attention Deficit Hyperactivity Disorder, schizophrenia, and personality disorders) may influence group differences observed in brain parameters of interest at a later stage in life. These findings should serve to increase our attention to early influences. Walhovd KB, Fjell AM, Brown TT, Kuperman JM, Chung Y, Hagler DJ Jr, Roddey JC, Erhart M, McCabe C, Akshoomoff N, Amaral DG, Bloss CS, Libiger O, Schork NJ, Darst BF, Casey BJ, Chang L, Ernst TM, Frazier J, Gruen JR, Kaufmann WE, Murray SS, van Zijl P, Mostofsky S, Dale AM; Pediatric Imaging, Neurocognition, and Genetics Study. Long-term influence of normal variation in neonatal characteristics on human brain development. Proc Natl Acad Sci U S A. 2012 Dec 4; 109(49): 20089-20094.

Effects of Abstinence in Adolescent Tobacco Smokers: Withdrawal Symptoms, Urge, Affect, and Cue Reactivity The aim of this study was to evaluate abstinence effects in adolescent daily smokers by examining the effects of experimentally manipulated acute smoking abstinence on measures including: (a) withdrawal symptoms, (b) reactive irritability, (c) smoking urges, (d) affect, and (e) responses to smoking cues. Participants (ages 13-19, 74 daily smokers, and 22 nonsmokers) completed baseline questionnaires and laboratory assessments (Session 1) and returned 1-4 days later to repeat the laboratory assessments (Session 2); half of the smokers were randomly assigned to overnight tobacco abstinence preceding Session 2. During Session 2, abstinent smokers reported significantly greater increases in withdrawal symptoms, smoking urges, and negative affect compared with smokers who did not abstain and compared with nonsmokers. Although there was not a significant effect of abstinence on differential reactivity to smoking versus neutral cues, abstinence did result in significantly increased peak provoked urges and negative effect. There was not a significant effect of abstinence on positive affect or reactive irritability. The results suggest that adolescents experience increases in withdrawal symptoms, smoking urges (un-cued and peak provoked), and negative affect (un-cued and peak provoked) after acute smoking abstinence, but do not experience the increases in reactive irritability or decreases in positive affect that have been shown in adult smokers. Overall findings support the withdrawal relief and negative reinforcement models of smoking maintenance in adolescents and point to withdrawal, urge, and negative affect as important targets for treatment. Bidwell LC, Leventhal AM, Tidey JW, Brazil L, Niaura RS, Colby SM. Effects of abstinence in adolescent tobacco smokers: withdrawal symptoms, urge, affect, and cue reactivity. Nicotine Tob Res. 2013 Feb; 15(2): 457-464.

Psychopathic Traits and Their Association with Adjustment Problems in Girls Psychopathic traits, and specifically callous-unemotional (CU) traits, are associated with a variety of adverse outcomes in adolescence and adulthood. The majority of research in this area has focused on men and boys, though there is some evidence that psychopathy is expressed differently in girls and women. Accordingly, the purpose of this study was to test if the relationships of callous-unemotional (CU) traits with adjustment differed between girls and boys at risk for antisocial behavior. The sample was composed of children whose biological father had past or current alcohol or drug problems. A total of 234 children (116 boys, 118 girls; ages 10-12) were rated by their parent or guardian on CU traits and overall adjustment. Boys were generally rated higher on measures of CU traits; however, these traits were more prominently related to adjustment problems

among girls. These results suggest that expression of psychopathic traits may have more negative effects on adjustment for girls than boys. One possible mechanism by which CU traits could be impacting adjustment in girls is by impairing interpersonal relationships. Charles NE, Acheson A, Mathias CW, Michael Furr R, Dougherty DM. Psychopathic traits and their association with adjustment problems in girls. Behav Sci Law. 2012 Sep-Oct; 30(5): 631-642.

Comparison of 12-Year-Old Children with Prenatal Exposure to Cocaine and Non-Exposed Controls on Caregiver Ratings of Executive Function Differences in caregiver reported executive function in 12-year-old children who were prenatally exposed to cocaine (PCE) compared to children who were not prenatally exposed to cocaine (NCE) were assessed. One hundred and sixty-nine PCE and 169 NCE, primarily African-American, low socioeconomic status children participated in a prospective longitudinal study. The Behavior Rating Inventory of Executive Function (BRIEF) Parent Form was administered. Two broadband BRIEF scores (Behavioral Regulation Index (BRI) and Metacognition Index (MI)) and a summary Global Executive Composite (GEC) were computed. Multiple and logistic regression analyses were used to assess the effects of amount of PCE on executive function, controlling for covariates including caregiver (rater) psychological distress, child's gender and other prenatal drug exposure variables. After adjustment for covariates, amount of PCE was associated with the GEC and two MI subscales, Plan/Organize and Monitor, with heavier exposure associated with more problems of executive function. An amount of PCE by gender interaction revealed amount of PCE effects in other remaining subscales of the MI (Initiate, Working Memory, and Organization of Materials) only among girls. Head circumference did not mediate the effects of cocaine on outcomes. Higher current caregiver psychological distress levels were independently associated with poorer ratings on the executive function scales. Assessment and targeted interventions to improve metacognitive processes are recommended for girls who were prenatally exposed to cocaine. Minnes S, Singer LT, Min MO, Lang AM, Ben-Harush A, Short E, Wu M. Comparison of 12-Year-old children with prenatal exposure to cocaine and non-exposed controls on caregiver ratings of executive function. J Youth Adolesc. 2013 Feb 20. [Epub ahead of print].

Adolescent Substance Use in the Multimodal Treatment Study of Attention Deficit/ Hyperactivity Disorder (ADHD) (MTA) as a Function of Childhood ADHD, Random Assignment to Childhood Treatments, and Subsequent Medication The purpose of this study was to determine long-term effects on substance use and substance use disorder (SUD), up to 8 years after childhood enrollment, of the randomly assigned 14-month treatments in the multisite Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA; n = 436); to test whether medication at follow-up, cumulative psychostimulant treatment over time, or both relate to substance use/SUD; and to compare substance use/SUD in the ADHD sample to the non-ADHD childhood classmate comparison group (n = 261). Mixed-effects regression models with planned contrasts were used for all tests except the important cumulative stimulant treatment question, for which propensity score matching analysis was used. The originally randomized treatment groups did not differ significantly on substance use/SUD by the 8-year follow-up or earlier (mean age = 17 years). Neither medication at follow-up (mostly stimulants) nor cumulative stimulant treatment was associated with adolescent substance use/SUD. Substance use at all time points, including use of two or more substances and SUD, were each greater in the ADHD than in the non-ADHD samples, regardless of sex. Medication for ADHD did not protect from, or contribute to, visible risk of substance use or SUD by adolescence, whether analyzed as randomized treatment assignment in childhood, as medication at follow-up, or as cumulative stimulant treatment over an 8-year follow-up from childhood. These results suggest the need to identify alternative or

adjunctive adolescent-focused approaches to substance abuse prevention and treatment for boys and girls with ADHD, especially given their increased risk for use and abuse of multiple substances that is not improved with stimulant medication. Clinical trial registration information-Multimodal Treatment Study of Children With Attention Deficit and Hyperactivity Disorder (MTA); http://clinical trials.gov/; NCT00000388. Molina BS, Hinshaw SP, Eugene Arnold L, Swanson JM, Pelham WE, Hechtman L, Hoza B, Epstein JN, Wigal T, Abikoff HB, Greenhill LL, Jensen PS, Wells KC, Vitiello B, Gibbons RD, Howard A, Houck PR, Hur K, Lu B, Marcus S; MTA Cooperative Group. Adolescent substance use in the multimodal treatment study of attention-deficit/hyperactivity disorder (ADHD) (MTA) as a function of childhood ADHD, random assignment to childhood treatments, and subsequent medication. J Am Acad Child Adolesc Psychiatry. 2013 Mar; 52(3): 250-263.

CLINICAL NEUROSCIENCE RESEARCH

An fMRI-based Neurologic Signature of Physical Pain Persistent pain is measured by means of self-report, the sole reliance on which hampers diagnosis and treatment. Functional magnetic resonance imaging (fMRI) holds promise for identifying objective measures of pain, but brain measures that are sensitive and specific to physical pain have not yet been identified. In four studies involving a total of 114 participants, the authors developed an fMRI-based measure that predicts pain intensity at the level of the individual person. In study 1, they used machine-learning analyses to identify a pattern of fMRI activity across brain regions--a neurologic signature--that was associated with heat-induced pain. The pattern included the thalamus, the posterior and anterior insulae, the secondary somatosensory cortex, the anterior cingulate cortex, the periaqueductal gray matter, and other regions. In study 2, the authors tested the sensitivity and specificity of the signature to pain versus warmth in a new sample. In study 3, they assessed specificity relative to social pain, which activates many of the same brain regions as physical pain. In study 4, they assessed the responsiveness of the measure to the analgesic agent remifentanil. Results indicated that in study 1, the neurologic signature showed sensitivity and specificity of 94% or more (95% confidence interval [CI], 89 to 98) in discriminating painful heat from nonpainful warmth, pain anticipation, and pain recall. In study 2, the signature discriminated between painful heat and nonpainful warmth with 93% sensitivity and specificity (95% CI, 84 to 100). In study 3, it discriminated between physical pain and social pain with 85% sensitivity (95% CI, 76 to 94) and 73% specificity (95% CI, 61 to 84) and with 95% sensitivity and specificity in a forced-choice test of which of two conditions was more painful. In study 4, the strength of the signature response was substantially reduced when remifentanil was administered. The authors conclude that it is possible to use fMRI to assess pain elicited by noxious heat in healthy persons. Future studies are needed to assess whether the signature predicts clinical pain. Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-based neurologic signature of physical pain. N Engl J Med. 2013 Apr 11; 368(15): 1388-1397.

Predominance Of D2 Receptors In Mediating Dopamine's Effects In Brain Metabolism: Effects Of Alcoholism Dopamine signals through D1-like and D2-like receptors, which can stimulate or inhibit, respectively, neuronal activity. Here the authors assessed the balance between D1 or D2 receptor signaling in the human brain and how it is affected in alcoholism. Using PET, they measured the relationship between changes in dopamine and brain glucose metabolism induced by methylphenidate in controls and alcoholics. They show that methylphenidate induced significant DA increases in striatum, amygdala, and medial orbitofrontal cortex, whereas it decreased metabolism in these brain regions. Methylphenidate-induced dopamine increases were greater in controls than in alcoholics, whereas methylphenidate-induced metabolic decreases were greater in alcoholics. For both groups, methylphenidate-induced dopamine increases were associated with decreases in regional brain metabolism, and the correlations were strongest in subthalamic nuclei, anterior cingulate, and medial orbitofrontal cortex. These correlations were more extensive and robust and the slopes steeper in alcoholics than in controls despite their attenuated dopamine responses to methylphenidate, which suggests an impaired modulation of dopamine signals in the brain of alcoholic subjects. These findings are consistent with a predominant inhibitory effect of dopamine in the human brain that is likely mediated by the prominence of dopamine D2/D3 receptors. Volkow ND, Tomasi D, Wang GJ, Telang F, Fowler JS, Logan J, Maynard LJ, Wong CT. Predominance of D2 receptors in mediating dopamine's effects in brain metabolism: Effects of alcoholism J Neurosci. 2013 Mar 6; 33(10): 4527-4535. doi: 10.1523/JNEUROSCI.5261-12.2013.

Wavelet-Transformed Temporal Cerebral Blood Flow Signals during Attempted Inhibition of Cue-Induced Cocaine Craving Distinguish Prognostic Phenotypes Cocaine addicted patients with positive cocaine urine status at treatment entry are far less likely to have a successful treatment outcome. This work aims to identify brain substrates that can distinguish this group of patients from their cocaine-negative counterparts in order to better understand this clinical phenotype. Going a step beyond conventional functional connectivity, we used wavelet transform coherence (WTC) to determine in which ways the temporal pattern of fMRI cerebral blood flow (CBF) signals during attempted inhibition of cue-induced cocaine craving may differ between these two groups. Using a critical node in motivational circuitry, amygdala, as a seed, whole brain correlations for the entire sample revealed a functional connection with the dorsal cingulate. Next, WTC maps of CBF were constructed for each individual, characterizing the temporal patterns between these two regions during craving inhibition. As revealed by WTC, during attempted craving inhibition, the cocaine-negative subjects had significantly stronger and longer negative coherence between the amygdala and the dorsal cingulate, as compared to the cocaine-positive subjects. This relationship was neither evident in the resting state nor between two regions unrelated to inhibition processes. The duration and strength of negative coherence calculated from wavelet-transformed CBF provide an objective and well-defined way to characterize brain responses during attempted inhibition of cue-induced craving, at the level of the individual. The stronger and sustained negative coherence in CBF between motivational (amygdala) and modulatory (dorsal cingulate) regions in cocaine-negative subjects may be a critical brain strength that fosters improved craving inhibition and thus, better clinical outcome. Lam SC, Wang Z, Li Y, Franklin T, O'Brien C, Magland J, Childress AR. Wavelet-transformed temporal cerebral blood flow signals during attempted inhibition of cue-induced cocaine craving distinguish prognostic phenotypes. Drug Alcohol Depend. 2013 Feb 1; 128(1-2): 140-147.

Error Processing and Gender-Shared and -Specific Neural Predictors Of Relapse In Cocaine Dependence Deficits in cognitive control are implicated in cocaine dependence. Previously, combining functional magnetic resonance imaging and a stop signal task, the authors demonstrated altered cognitive control in cocaine-dependent individuals. However, the clinical implications of these cross-sectional findings and, in particular, whether the changes were associated with relapse to drug use, were not clear. In a prospective study, the authors recruited 97 treatment-seeking individuals with cocaine dependence to perform the stop signal task during functional magnetic resonance imaging and participate in follow-up assessments for 3 months, during which time cocaine use was evaluated with timeline follow back and ascertained by urine toxicology tests. Functional magnetic resonance imaging data were analysed using general linear models as implemented in Statistical Parametric Mapping 8, with the contrast 'stop error greater than stop success trials' to index error processing. Using voxelwise analysis with logistic and Cox regressions, we identified brain activations of error processing that predict relapse and time to relapse. In females, decreased error-related activations of the thalamus and dorsal anterior cingulate cortex predicted relapse and an earlier time to relapse. In males, decreased error-related activations of the dorsal anterior cingulate cortex and left insula predicted relapse and an earlier time to relapse. These regional activations were validated with data resampling and predicted relapse with an average area under the curve of 0.849 in receiver operating characteristic analyses. These findings provide direct evidence linking deficits in cognitive control to clinical outcome in a moderate-sized cohort of cocaine-dependent individuals. These results may provide a useful basis for future studies to examine how psychosocial factors interact with cognitive control to determine drug use and to evaluate the efficacy of pharmacological or behavioural treatment in remediating deficits of cognitive control in cocaine addicts. Luo X, Zhang S, Hu S, Bednarski SR, Erdman E, Farr OM,

Hong KI, Sinha R, Mazure CM, Li CS. Error processing and gender-shared and -specific neural predictors of relapse in cocaine dependence. Brain. 2013 Apr; 136(Pt 4): 1231-1244. doi: 10.1093/brain/awt040. Epub 2013 Mar 12.

Individual Differences In Anterior Cingulate Activation Associated With Attentional Bias Predict Cocaine Use After Treatment Drug-dependent patients often relapse into drug use after treatment. Behavioral studies show that enhanced attentional bias to drug cues is a precursor of relapse. The present functional magnetic resonance imaging (fMRI) study examined whether brain regions involved in attentional bias are predictive of cocaine use after treatment. Attentional bias-related brain activity was measured-with a cocaine Stroop task-in cocaine-dependent patients during their first week in detoxification treatment and was used to predict cocaine use at 3-month follow-up. The predictive value of attentional bias-related brain activity in a priori defined regions of interest, in addition to other measures such as self-reports of substance severity, craving, and behavioral attentional bias were examined. The results show that craving in the week before treatment and individual variability in attentional bias-related activity in the dorsal anterior cingulate cortex (dACC) were significant predictors of days of cocaine use at 3-month follow-up and accounted for 45% in explained variance. Brain activity in the dACC uniquely contributed 22% of explained variance to the prediction model. These findings suggest that hyperactive attentional bias-related brain activity in the dACC might be a biomarker of relapse vulnerability as early as in the first week of detoxification treatment. Ultimately, this may help to develop individually tailored treatment interventions to reduce relapse risk. Marhe R, Luijten M, van de Wetering BJ, Smits M, Franken IH. Individual differences in anterior cingulate activation associated with attentional bias predict cocaine use after treatment. Neuropsychopharmacology. 2013 May; 38(6): 1085-1093.

Prefrontal and Limbic Resting State Brain Network Functional Connectivity Differs between Nicotine-Dependent Smokers and Non-Smoking Controls Brain dysfunction in prefrontal cortex (PFC) and dorsal striatum (DS) contributes to habitual drug use. These regions are constituents of brain networks thought to be involved in drug addiction. To investigate whether networks containing these regions differ between nicotine dependent female smokers and age-matched female non-smokers, the authors employed functional MRI (fMRI) at rest. Data were processed with independent component analysis (ICA) to identify resting state networks (RSNs). The authors identified a subcortical limbic network and three discrete PFC networks: a medial prefrontal cortex (mPFC) network and right and left lateralized fronto-parietal networks common to all subjects. They then compared these RSNs between smokers and non-smokers using a dual regression approach. The results indicated that smokers had greater coupling versus non-smokers between left fronto-parietal and mPFC networks. Smokers with the greatest mPFC-left fronto-parietal coupling had the most DS smoking cue reactivity as measured during an fMRI smoking cue reactivity paradigm. This may be important because the DS plays a critical role in maintaining drug-cue associations. Furthermore, subcortical limbic network amplitude was greater in smokers. These results suggest that prefrontal brain networks are more strongly coupled in smokers, which could facilitate drug-cue responding. These data also are the first to document greater reward-related network fMRI amplitude in smokers. These findings suggest that resting state PFC network interactions and limbic network amplitude can differentiate nicotine-dependent smokers from controls, and may serve as biomarkers for nicotine dependence severity and treatment efficacy. Janes AC, Nickerson LD, Frederick B de B, Kaufman MJ. Prefrontal and limbic resting state brain network functional connectivity differs between nicotine-dependent smokers and non-smoking controls. Drug Alcohol Depend. 2012 Oct 1; 125(3): 252-259.

Gray-Matter Volume in Methamphetamine Dependence: Cigarette Smoking and Changes with Abstinence from Methamphetamine Group differences in brain structure between methamphetamine-dependent and healthy research participants have been reported, but findings in the literature present discrepancies. Although most methamphetamine-abusing individuals also smoke cigarettes, the effects of smoking on brain structure have not been distinguished from those of methamphetamine. Changes with abstinence from methamphetamine have also been relatively unexplored. This study, therefore, attempted to account for effects of smoking and brief abstinence from methamphetamine on gray-matter measures in methamphetamine-dependent research participants. Gray matter was measured using voxel-based morphometry in three groups: 18 control nonsmokers, 25 control smokers, and 39 methamphetamine-dependent smokers (methamphetamine-abstinent 4-7 days). Subgroups of methamphetamine-dependent and control participants (n=12/group) were scanned twice to determine change in gray matter over the first month of methamphetamine abstinence. Compared with Control Nonsmokers, Control Smokers and Methamphetamine-dependent Smokers had smaller gray-matter volume in the orbitofrontal cortex and caudate nucleus. Methamphetamine-dependent Smokers also had smaller gray-matter volumes in frontal, parietal and temporal cortices than Control Nonsmokers or Smokers, and smaller gray-matter volume in insula than control nonsmokers. Longitudinal assessment revealed gray matter increases in cortical regions (inferior frontal, angular, and superior temporal gyri, precuneus, insula, occipital pole) in methamphetamine-dependent but not control participants; the cerebellum showed a decrease. Gray-matter volume deficits in the orbitofrontal cortex and caudate of methamphetamine-dependent individuals may be in part attributable to cigarette smoking or pre-morbid conditions. Increase in gray matter with methamphetamine abstinence suggests that some gray-matter deficits are partially attributable to methamphetamine abuse. Morales AM, Lee B, Hellemann G, O'Neill J, London ED. Gray-matter volume in methamphetamine dependence: Cigarette smoking and changes with abstinence from methamphetamine. Drug Alcohol Depend. 2012 Oct 1; 125(3): 230-238.

EEG Responses to Cocaine Images Better Predictor of Choice to View Cocaine Images than Self-Reported Liking: A Means to Circumvent Impaired Insight in Addiction An important goal of addiction research and treatment is to predict behavioural responses to drug-related stimuli. This goal is especially important for patients with impaired insight, which can interfere with therapeutic interventions and potentially invalidate self-report questionnaires. This research tested (i) whether event-related potentials, specifically the late positive potential, predict choice to view cocaine images in cocaine addiction; and (ii) whether such behaviour prediction differs by insight (operationalized in this study as self-awareness of image choice). Fifty-nine cocaine abusers and 32 healthy controls provided data for the following laboratory components that were completed in a fixed-sequence (to establish prediction): (i) event-related potential recordings while passively viewing pleasant, unpleasant, neutral and cocaine images, during which early (400-1000 ms) and late (1000-2000 ms) window late positive potentials were collected; (ii) self-reported arousal ratings for each picture; and (iii) two previously validated tasks: one to assess choice for viewing these same images, and the other to group cocaine abusers by insight. Results showed that pleasant-related late positive potentials and arousal ratings predicted pleasant choice (the choice to view pleasant pictures) in all subjects, validating the method. In the cocaine abusers, the predictive ability of the late positive potentials and arousal ratings depended on insight. Cocaine-related late positive potentials better predicted cocaine image choice in cocaine abusers with impaired insight. Another emotion-relevant event-related potential component (the early posterior negativity) did not show these results, indicating specificity of the late positive potential. In contrast, arousal ratings better predicted respective cocaine image choice (and actual cocaine use severity) in cocaine abusers with

intact insight. Taken together, the late positive potential could serve as a biomarker to help predict drug-related choice--and possibly associated behaviours (e.g. drug seeking in natural settings, relapse after treatment)--when insight (and self-report) is compromised. Moeller SJ, Hajcak G, Parvaz MA, Dunning JP, Volkow ND, Goldstein RZ. Psychophysiological prediction of choice: relevance to insight and drug addiction. Brain. 2012 Nov; 135(Pt 11): 3481-3494.

Resting-State Activity in the Left Executive Control Network is Associated with Behavioral Approach and is Increased in Substance Dependence Individuals with drug addictions report increased willingness to approach rewards. Approach behaviors are thought to involve executive control processes and are more strongly represented in the left compared to right prefrontal cortex. A direct link between approach tendencies and left hemisphere activity has not been shown in the resting brain. We hypothesized that compared to controls, substance dependent individuals (SDI) would have greater left hemisphere activity in the left executive control network (ECN) at rest. Twenty-five SDI and 25 controls completed a Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) questionnaire and underwent a resting-state fMRI scan. Group independent component analysis was performed. The authors used template matching to identify the left and right ECN separately and compared the corresponding components across groups. Across group, BAS scores were correlated with signal fluctuations in the left ECN and BIS scores with right ECN. BAS scores were higher in SDI compared to controls ($p<.003$) and correlated with signal fluctuation in the left ECN. SDI showed significantly more activity than controls in the left prefrontal cortex of the left ECN. Conversely, SDI showed less activity than controls in the right prefrontal cortex of the right ECN. Results from this study suggest that approach tendencies are related to the left ECN, even during rest. Higher resting-state signal in the left ECN may play a role in heightened approach tendencies that contribute to drug-seeking behavior. Krmpotich TD, Tregellas JR, Thompson LL, Banich MT, Klenk AM, Tanabe JL. Resting-state activity in the left executive control network is associated with behavioral approach and is increased in substance dependence. Drug Alcohol Depend. 2013 Apr 1; 129(1-2): 1-7.

Effects of Varenicline on Abstinence and Smoking Reward Following a Programmed Lapse Varenicline (Chantix®) is an efficacious first-line medication for smoking cessation. Studies suggest that one mechanism by which varenicline facilitates sustained smoking abstinence is by reducing the likelihood of relapse to smoking when a lapse, or slip, occurs during a quit attempt. The present study extends this line of research by conducting a prospective laboratory study to examine the relapse prevention effects of varenicline following a programmed lapse. Daily smokers ($N = 47$) completed a 5-week outpatient study in which they were randomized to receive varenicline or placebo. The first week was a medication induction period that was immediately followed by a 4-week quit attempt. A programmed lapse (2 cigarettes smoked in the laboratory) occurred on the second day of the quit attempt. Participants receiving varenicline were slower to relapse and had greater total abstinence rates following lapse exposure. Participants in the varenicline group rated lapse cigarettes lower on measures of reward and intoxication and showed increased behavioral economic demand elasticity for cigarettes (reduced cigarette purchasing at higher prices) compared with those receiving placebo. These results demonstrate a relapse prevention effect of varenicline following smoking lapse exposure and suggest that an attenuation of reward from smoking and the blunting of subjective effects of smoking may underlie and/or contribute to this effect. McClure EA, Vandrey RG, Johnson MW, Stitzer ML. Effects of varenicline on abstinence and smoking reward following a programmed lapse. Nicotine Tob Res. 2013 Jan; 15(1): 139-148.

Fitness Supplements as a Gateway Substance for Anabolic-Androgenic Steroid Use
Approximately 3.0% of young Americans have used anabolic-androgenic steroids (AAS). A traditional model of adolescent substance use, the gateway hypothesis, suggests that drug use follows a chronological, causal sequence, whereby initial use of a specific drug leads to an increased likelihood of future drug use. Therefore, the use of illicit appearance and performance enhancing drugs (APED), such as AASs, also follows an analogous progression, whereby legal APEDs, (e.g., nutritional supplements) precedes illicit APED use. The authors examined the relationship between nutritional supplement use, beliefs about APEDs, and APED use in 201 male (n = 100) and female (n = 101) undergraduates. Participants completed measures of muscle dysmorphia (MDDI), body checking (BCQ, MBCQ), eating disorder symptoms (EDE-Q), perfectionism (FMPS), positive beliefs about the efficacy-safety of AAS use and APED use patterns. A series of covariance structure models (CSM) showed body image disturbance, compulsive exercise, illicit drug use, and perfectionism, independent of gender, were significant predictors of positive beliefs about AAS. Those who used both fat burning and muscle building supplements reported the strongest beliefs in AAS efficacy-safety, which was associated with higher likelihood of current illicit APED use. There was evidence of significant indirect relationships between supplement use and illicit APED use through contact with other AAS users and beliefs about AAS. The potential role for nutritional supplement use in the initiation of illegal APED use is discussed. Future prevention efforts may benefit from targeting legal APED users in youth. Hildebrandt T, Harty S, Langenbucher JW. Fitness supplements as a gateway substance for anabolic-androgenic steroid use. Psychol Addict Behav. 2012 Dec; 26(4): 955-962.

Working Memory and Speed of Information Processing in Chronic Khat Users: Preliminary Findings To date there are very few laboratory data available regarding the long-term effect of the psychostimulant khat on human neurocognitive functioning. The purpose of the present study was to assess whether chronic khat users would demonstrate impairments in working memory and speed of information processing compared to control subjects. Working memory was assessed using the forward and backward digit span test. Speed of information processing was assessed using the Digit Symbol Substitution Test. Results of the present study indicate that chronic khat use may have a long-term deleterious effect on working memory, particularly on digit backwards measures of short-term/working memory. The finding is consistent with results seen by several investigators in samples of methamphetamine users. Hoffman R, Al'absi M. Working memory and speed of information processing in chronic khat users: Preliminary findings.Eur Addict Res. 2013;19(1): 1-6.

Personality Trait Predictors of Placebo Analgesia and Neurobiological Correlates Personality traits have been shown to interact with environmental cues to modulate biological responses including treatment responses, and potentially having a role in the formation of placebo effects. Here, the authors assessed psychological traits in 50 healthy controls as to their capacity to predict placebo analgesic effects, placebo-induced activation of μ-opioid neurotransmission and changes in cortisol plasma levels during a sustained experimental pain challenge (hypertonic saline infused in the masseter muscle) with and without placebo administration. Statistical analyses showed that an aggregate of scores from Ego-Resiliency, NEO Altruism, NEO Straightforwardness (positive predictors) and NEO Angry Hostility (negative predictor) scales accounted for 25% of the variance in placebo analgesic responses. Molecular imaging showed that subjects scoring above the median in a composite of those trait measures also presented greater placebo-induced activation of μ-opioid neurotransmission in the subgenual and dorsal anterior cingulate cortex (ACC), orbitofrontal cortex, insula, nucleus accumbens, amygdala and periaqueductal gray (PAG). Endogenous opioid release in the dorsal ACC and PAG was positively correlated with placebo-induced reductions in pain ratings.

Significant reductions in cortisol levels were observed during placebo administration and were positively correlated with decreases in pain ratings, μ-opioid system activation in the dorsal ACC and PAG, and as a trend, negatively with NEO Angry Hostility scores. These results show that personality traits explain a substantial proportion of the variance in placebo analgesic responses and are further associated with activations in endogenous opioid neurotransmission, and as a trend cortisol plasma levels. These initial data, if replicated in larger sample, suggest that simple trait measures easily deployable in the field could be utilized to reduce variability in clinical trials, but may also point to measures of individual resiliency in the face of aversive stimuli such as persistent pain and potentially other stressors. Peciña M, Azhar H, Love TM, Lu T, Fredrickson BL, Stohler CS, Zubieta JK. Personality trait predictors of placebo analgesia and neurobiological correlates. Neuropsychopharmacology 2013 Mar; 38(4): 639-646.

Lower Cognitive Reserve in the Aging Human Immunodeficiency Virus-Infected Brain More HIV-infected individuals are living longer; however, how their brain function is affected by aging is not well understood. One hundred twenty-two men (56 seronegative control [SN] subjects, 37 HIV subjects with normal cognition [HIV+NC], 29 with HIV-associated neurocognitive disorder [HAND]) performed neuropsychological tests and had acceptable functional magnetic resonance imaging scans at 3 Tesla during tasks with increasing attentional load. With older age, SN and HIV+NC subjects showed increased activation in the left posterior (reserve, "bottom-up") attention network for low attentional-load tasks, and further increased activation in the left posterior and anterior ("top-down") attention network on intermediate (HIV+NC only) and high attentional-load tasks. HAND subjects had only age-dependent decreases in activation. Age-dependent changes in brain activation differed between the 3 groups, primarily in the left frontal regions (despite similar brain atrophy). HIV and aging act synergistically or interactively to exacerbate brain activation abnormalities in different brain regions, suggestive of a neuroadaptive mechanism in the attention network to compensate for declined neural efficiency. While the SN and HIV+NC subjects compensated for their declining attention with age by using reserve and "top-down" attentional networks, older HAND subjects were unable to compensate, which resulted in cognitive decline. Chang L, Holt JL, Yakupov R, Jiang CS, Ernst T. Lower cognitive reserve in the aging human immunodeficiency virus-infected brain. Neurobiol Aging. 2013 Apr; 34(4): 1240-1253.

Reduced rsFC Strength Associated with Nicotine Addiction Severity in both Non-psychiatrically Ill and in SZ Smokers Schizophrenia (SZ) is associated with high rates of smoking. The authors previously found that resting state functional connectivity (rsFC) between the dorsal anterior cingulate (dACC) and striatum is independently associated with nicotine addiction and psychiatric illness. Since the insula is implicated in nicotine dependence, they hypothesized that SZ smokers will have greater dysfunction in smoking-related insular and dACC circuits than normal control smokers (NC) independent of smoking severity, consistent with an inherent disease-related weakening of smoking-related circuits. Nicotine challenge was used to demonstrate that decreased rsFC in identified circuits reflects addiction trait and is not affected by pharmacological state. Twenty-four NC smokers and 20 smokers with SZ matched on nicotine addiction severity participated in a resting state fMRI study and were scanned during two separate sessions while receiving a placebo or nicotine patch, in a randomized, cross-over design. Using individualized, anatomically defined anterior and posterior insula and dACC as regions of interest (ROI), whole brain rsFC was performed using each ROI as a seed. Significant negative correlations between smoking severity and rsFC between insula, dACC and striatum were found for both groups. Furthermore, smokers with SZ demonstrated additive reductions in circuit strength between the dACC and insula compared to NC smokers independent of smoking severity. Nicotine challenge

did not significantly alter rsFC in insula-dACC-striatal circuits. Reduced rsFC strength between the insula, dACC and striatum is associated with nicotine addiction severity in both non-psychiatrically ill and in SZ smokers. Decreased insula-dACC rsFC may index overlapping circuitry associated with smoking and SZ. Moran LV, Sampath H, Stein EA, Hong LE. Insular and anterior cingulate circuits in smokers with schizophrenia. Schizophr Res. 2012 Dec; 142(1-3): 223-229.

Altruism in Time: Social Temporal Discounting Differentiates Smokers from Problem Drinkers Recent studies on reinforcer valuation in social situations have informed research on mental illness. Social temporal discounting may be a way to examine effects of social context on the devaluation of delayed reinforcers. In prior research with non-drug-using groups, we demonstrated that individuals discount delayed rewards less rapidly (i.e., value the future more) for a group of which they are a member than they do for themselves alone. The current study examined how cigarette smoking and level of alcohol use relate to rates of delay and social temporal discounting. In this study, the authors used crowd-sourcing technology to contact a large number of individuals (N = 796). Some of these individuals were hazardous-to-harmful drinkers (n = 269), whereas others were non-problem drinkers (n = 523); some were smokers (n = 182), whereas others were nonsmokers (n = 614). Delay discounting questionnaires for individual rewards (me now, me later) and for group rewards (we now, we later; me now, we later) were used to measure individuals' discounting rates across various social contexts. The authors' analyses found that smokers discounted delayed rewards more rapidly than controls under all conditions. However, hazardous-to-harmful drinkers discounted delayed rewards significantly more rapidly than the non-problem drinkers under the individual condition, but not under the social conditions. This finding suggests that the use of different abused drugs may be associated with excessive discounting in the individual condition and has selective effects when discounting for a group in the social conditions. Bickel WK, Jarmolowicz DP, Mueller ET, Franck CT, Carrin C, Gatchalian KM. Altruism in time: Social temporal discounting differentiates smokers from problem drinkers. Psychopharmacology (Berl). 2012 Nov; 224(1): 109-120.

Methamphetamine Use and Neuropsychiatric Factors are Associated with Antiretroviral Non-adherence The present study assesses the impact of methamphetamine (METH) on antiretroviral therapy (ART) adherence among HIV+ persons, as well as examines the contribution of neurocognitive impairment and other neuropsychiatric factors [i.e., major depressive disorder (MDD), antisocial personality disorder (ASPD), and attention deficit disorder (ADHD)] for ART non-adherence. The authors examined HIV+ persons with DSM-IV-diagnosed lifetime history of METH abuse/dependence (HIV+ /METH+ ; n=67) as compared to HIV+ participants with no history of METH abuse/dependence (HIV+ /METH - ; n=50). Ancillary analyses compared these groups with a small group of HIV+ /METH+ persons with current METH abuse/dependence (HIV+ /CU METH+ ; n=8). Non-adherence was defined as self-report of any skipped ART dose in the last four days. Neurocognitive functioning was assessed with a comprehensive battery, covering seven neuropsychological domains. Lifetime METH diagnosis was associated with higher rates of detectable levels of plasma and CSF HIV RNA. When combing groups (i.e., METH+ and METH- participants), univariate analyses indicated co-occurring ADHD, ASPD, and MDD predicted ART non-adherence (p's < 0.10; not lifetime METH status or neurocognitive impairment). A significant multivariable model including these variables indicated that only MDD uniquely predicted ART non-adherence after controlling for the other variables ($p<0.05$). Ancillary analyses indicated that current METH users (use within 30 days) were significantly less adherent (50% prevalence of non-adherence) than lifetime METH+ users and HIV+ /METH- participants and that neurocognitive impairment was associated with non-adherence (p's < 0.05). METH use disorders are associated

with worse HIV disease outcomes and ART medication non-adherence. Interventions often target substance use behaviors alone to enhance antiretroviral treatment outcomes; however, in addition to targeting substance use behaviors, interventions to improve ART adherence may also need to address coexisting neuropsychiatric factors and cognitive impairment to improve ART medication taking. Moore DJ, Blackstone K, Woods SP, Ellis RJ, Atkinson JH, Heaton RK, Grant I, The Hnrc Group And The Tmarc Group. Methamphetamine use and neuropsychiatric factors are associated with antiretroviral non-adherence. AIDS Care. 2012 Dec; 24(12): 1504-1513.

Denicotinized Versus Average Nicotine Tobacco Cigarette Smoking Differentially Releases Striatal Dopamine Nicotine has long been recognized as a necessary but insufficient component of tobacco cigarettes to maintain a psychophysiological need to smoke. This study examined venous plasma concentrations effects of nicotine in cigarette smoking after overnight abstinence to release striatal dopamine (DA). Twenty-two male smokers smoked either denicotinized (denic) or average nicotine (nic) cigarettes under single blind conditions. Each was given [^{11}C]raclopride and scanned in a positron emission tomography (PET) facility. Smoking either denic or nic cigarettes released striatal DA. Denic cigarette smoking released DA primarily in the right striatum, whereas nic cigarette smoking released DA in both striata, but especially in the left. Increases in venous plasma nicotine concentrations correlated positively with increased DA release in the left caudate nucleus. Smoking denic cigarettes reduced craving as much as smoking nic cigarettes. Craving reduction after nic tobacco smoking correlated with increases in plasma nicotine. Non-nicotine factors in tobacco smoking produce important right brain effects. Nicotine is a pharmacological factor during tobacco smoking that releases bilateral striatal DA, but more in the left brain. Domino ED, Ni L, Domino JS, Yang W, Evans C, Guthrie S, Wang H, Koeppe RA, Zubieta J-K. Denicotinized versus average nicotine tobacco cigarette smoking differentially releases striatal dopamine. Nicotine Tob Res. 2013; 15 (1): 11-21.

The Interplay of Genes and Adolescent Development in Substance Use Disorders: Leveraging Findings from GWAS Meta-analyses to Test Developmental Hypotheses about Nicotine Consumption The present study evaluated gene by development interaction in cigarettes smoked per day (CPD) in a longitudinal community-representative sample (N = 3,231) of Caucasian twins measured at ages 14, 17, 20, and 24. Biometric heritability analyses show strong heritabilities and shared environmental influences, as well as cross-age genetic and shared environmental correlations. Single nucleotide polymorphisms (SNPs) previously associated with CPD according to meta-analysis were summed to create a SNP score. At best, the SNP score accounted for 1 % of the variance in CPD. The results suggest developmental moderation with a larger significant SNP score effect on CPD at ages 20 and 24, and smaller non-significant effect at ages 14 and 17. These results are consistent with the notion that nicotine-specific genetic substance use risk is less important at younger ages, and becomes more important as individuals age into adulthood. In a complementary analysis, the same nicotine-relevant SNP score was unrelated to the frequency of alcohol use at ages 14, 17, 20, or 24. These results indicate that the SNP score is specific to nicotine in this small sample and that increased exposure to nicotine at ages 20 and 24 does not influence the extent of concurrent or later alcohol use. Increased sample sizes and replication or meta-analysis are necessary to confirm these results. The methods and results illustrate the importance and difficulty of considering developmental processes in understanding the interplay of genes and environment. Scott I, Vrieze SI , McGue M, Iacono WG. The interplay of genes and adolescent development in substance use disorders: leveraging findings from GWAS meta-analyses to test developmental hypotheses about nicotine consumption. Hum Genet. 11 April 2012 [DOI: 10.1007/s00439-012-1167-1] .

Young Adults at Risk for Stimulant Dependence Show Reward Dysfunction During Reinforcement-based Decision Making While stimulant-dependent individuals continue to make risky decisions, in spite of poor outcomes, much less is known about decision-making characteristics of occasional stimulant users (OSU) at risk for developing stimulant dependence. This study examines whether OSU exhibit inefficient learning and execution of reinforced decision-outcome contingencies. Occasional stimulant users (n = 161) and stimulant-naïve comparison subjects (CTL) (n = 48) performed a Paper Scissors Rock task during functional magnetic resonance imaging. Selecting a particular option was associated with a predetermined probability of winning, which was altered repeatedly to examine neural and behavioral characteristics of reinforced contingencies. Occasional stimulant users displayed greater anterior insula, inferior frontal gyrus, and dorsal striatum activation than CTL during late trials when contingencies were familiar (as opposed to being learned) in the presence of comparable behavioral performance in both groups. Follow-up analyses demonstrated that during late trials: 1) OSU with high cannabis use displayed greater activation in these brain regions than CTL, whereas OSU with low cannabis use did not differ from the other two groups; and 2) OSU preferring cocaine exhibited greater anterior insula, inferior frontal gyrus, and dorsal striatum activation than CTL and also displayed higher activation in the former two regions than OSU who preferred prescription stimulants. Occasional stimulant users exhibit inefficient resource allocation during the execution of reinforced contingencies that may be a result of additive effects of cocaine and cannabis use. A critical next step is to establish whether this inefficiency predicts transition to stimulant dependence. Stewart JL, Flagan TM, May AC, Reske M, Simmons AN, Paulus MP. Young adults at risk for stimulant dependence show reward dysfunction during reinforcement-based decision making. Biological Psychiatry. 2013; 73(3): 235–241.

A Thalamocorticostriatal Dopamine Network for Psychostimulant-Enhanced Human Cognitive Flexibility Everyday life demands continuous flexibility in thought and behavior. The authors examined whether individual differences in dopamine function are related to variability in the effects of amphetamine on one aspect of flexibility: task switching. Forty healthy human participants performed a task-switching paradigm following placebo and oral amphetamine administration. [(18)F]fallypride was used to measure D2/D3 baseline receptor availability and amphetamine-stimulated dopamine release. The majority of the participants showed amphetamine-induced benefits through reductions in switch costs. However, such benefits were variable. Individuals with higher baseline thalamic and cortical receptor availability and striatal dopamine release showed greater reductions in switch costs following amphetamine than individuals with lower levels. The relationship between dopamine receptors and stimulant-enhanced flexibility was partially mediated by striatal dopamine release. These data indicate that the impact of the psychostimulant on cognitive flexibility is influenced by the status of dopamine within a thalamocorticostriatal network. Beyond demonstrating a link between this dopaminergic network and the enhancement in task switching, these neural measures accounted for unique variance in predicting the psychostimulant-induced cognitive enhancement. These results suggest that there may be measurable aspects of variability in the dopamine system that predispose certain individuals to benefit from and hence use psychostimulants for cognitive enhancement. Samanez-Larkin GR, Buckholtz JW, Cowan RL, Woodward ND, Li R, Ansari MS, Arrington CM, Baldwin RM, Smith CE, Treadwa MT, Kessler RM, Zald DH. A Thalamocorticostriatal dopamine network for psychostimulant-enhanced human cognitive flexibility. Biological Psychiatry. 2012; [DOI: 10.1016/j.biopsych.2012.10.032]. [Epub ahead of print].

Imaging Dopamine Transmission in the Frontal Cortex: a Simultaneous Microdialysis and [(11)C]FLB 457 PET Study In a recent human positron emission tomography (PET) study the authors demonstrated the ability to detect amphetamine-induced dopamine (DA) release in the prefrontal cortex as a reduction in the binding of the DA D(2/3) radioligand [(11)C]FLB 457. A key requirement for validating this paradigm for use in clinical studies is demonstrating that the changes in [(11)C]FLB 457 binding observed with PET following amphetamine are related to changes in dialysate DA concentration as measured with microdialysis. Microdialysis and PET experiments were performed to compare, in five rhesus monkeys, amphetamine-induced DA release and [(11)C]FLB 457 displacement in the frontal cortex after three doses of amphetamine (0.3 mg/kg, 0.5 mg/kg and 1.0 mg/kg). Amphetamine led to a significant dose-dependent increase in dialysate (0.3 mg/kg): 999±287%; 0.5 mg/kg): 1320±432%; 1.0 mg/kg: 2355±1026%) as measured with microdialysis and decrease in [(11)C]FLB 457 binding potential (BP(ND,) 0.3 mg/kg: -6±6%; 0.5 mg/kg): -16±4%; 1.0 mg/kg: -24±2%) as measured with PET. The relationship between amphetamine-induced peak ΔDA and Δ[(11)C]FLB 457 BP(ND) in the frontal cortex was linear. The results of this study clearly demonstrate that the magnitude of dialysate DA release is correlated with the magnitude of the reduction in [(11)C]FLB 457 BP(ND) in the frontal cortex. The use of the [(11)C]FLB 457-amphetamine imaging paradigm in humans should allow for characterization of prefrontal cortical DA release in neuropsychiatric disorders such as schizophrenia and addiction. Narendran R, Jedema HP, Lopresti BJ, Mason NS, Gurnsey K, Ruszkiewicz J, Chen C-M, Deuitch L, Frankle WG, Bradberry CW. Imaging Dopamine Transmission in the frontal cortex: a simultaneous microdialysis and [(11)C]FLB 457 PET study. Molecular Psychiatry. 2013. [DOI: 10.1038/mp.2013.9]. [Epub ahead of print].

Nicotine Content and Abstinence State Have Different Effects on Subjective Ratings of Positive Versus Negative Reinforcement from Smoking Despite the well-known adverse health consequences of smoking, approximately 20% of US adults smoke tobacco cigarettes. Much of the research on smoking reinforcement and the maintenance of tobacco smoking behavior has focused on nicotine; however, a number of other non-nicotine factors are likely to influence the reinforcing effects of smoked tobacco. A growing number of studies suggest that non-nicotine factors, through many pairings with nicotine, are partially responsible for the reinforcing effect of smoking. Additionally, both clinical studies and preclinical advances in our understanding of nicotinic receptor regulation suggest that abstinence from smoking may influence smoking reinforcement. These experiments were conducted for 2 reasons: to validate a MRI-compatible cigarette smoking device; and to simultaneously investigate the impact of nicotine, smoking-associated conditioned reinforcers, and smoking abstinence state on subjective ratings of smoking reinforcement. Participants smoked nicotine and placebo cigarettes through an fMRI compatible device in an overnight-abstinent state or in a nonabstinent state, after having smoked a cigarette 25minutes prior. Outcome measures were within-subject changes in physiology and subjective ratings of craving and drug effect during the smoking of nicotine or placebo cigarettes on different days in both abstinence states. Cigarette type (nicotine vs. placebo) had a significant effect on positive subjective ratings of smoking reinforcement (“High”, “Like Drug”, “Feel Drug”; nicotine>placebo). In contrast, abstinence state was found to have significant effects on both positive and negative ratings of smoking reinforcement (“Crave”, “Anxiety”, “Irritability”; abstinence>nonabstinence). Interaction effects between abstinence and nicotine provide clues about the importance of neuroadaptive mechanisms operating in dependence, as well as the impact of conditioned reinforcement on subjective ratings of smoking-induced high. Lindsey KP, Bracken BK, Maclean RR, Ryan ET, Lukas SE, Frederick BD. Nicotine content and abstinence state have different effects on subjective

ratings of positive versus negative reinforcement from smoking. Pharmacology, Biochemistry, and Behavior. 2013; 103(4): 710–716.

Does COMT Genotype Influence the Effects of D-amphetamine on Executive Functioning? In a widely cited study, Mattay et al. reported that amphetamine (0.25 mg/kg oral, or 17 mg for a 68 kg individual) impaired behavioral and brain indices of executive functioning, measured using the Wisconsin Card Sorting Task (WCST) and N-Back working memory task, in 6 individuals homozygous for the met allele of the val158met polymorphism in the catechol-O-methyltransferase (COMT) gene, whereas it improved executive functioning in 10 individuals homozygous for the more active val allele. The authors attempted to replicate their behavioral findings in a larger sample, using similar executive functioning tasks and a broader range of amphetamine doses. Over four sessions, n = 200 healthy normal adults received oral placebo, d-amphetamine 5, 10, and 20 mg (average of 0.07, 0.15 and 0.29 mg/kg), under counterbalanced double-blind conditions and completed WCST and N-back tests of executive functioning. Amphetamine had typical effects on blood pressure and processing speed but did not affect executive functioning. COMT genotype (val158met) was not related to executive functioning under placebo or amphetamine conditions, even when we compared only the homozygous val/val and met/met genotypes at the highest dose of amphetamine (20 mg). Thus, the authors were not able to replicate the behavioral interaction between COMT and amphetamine seen in Mattay et al. The authors discuss possible differences between the studies and the implications of their findings for the use of COMT genotyping to predict clinical responses to dopaminergic drugs, and the use of intermediate phenotypes in genetic research. Wardle MC, Hart AB, Palmer AA, Wit H de. Does COMT genotype influence the effects of D-amphetamine on executive functioning? Genes, Brain, and Behavior. 2013; 12(1): 13–20.

EPIDEMIOLOGY RESEARCH

The Relationship of Dysthymia, Minor Depression, and Gender to Changes in Smoking for Current and Former Smokers: Longitudinal Evaluation in the U.S. Population Although data clearly link major depression and smoking, little is known about the association between dysthymia and minor depression and smoking behavior. The current study examined changes in smoking over 3 years for current and former smokers with and without dysthymia and minor depression. Participants who were current or former daily cigarette smokers at Wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions and completed the Wave 2 assessment were included in these analyses (n=11,973; 46% female). Analyses examined the main and gender-specific effects of current dysthymia, lifetime dysthymia, and minor depression (a single diagnostic category that denoted current and/or lifetime prevalence) on continued smoking for Wave 1 current daily smokers and continued abstinence for Wave 1 former daily smokers. RESULTS: Wave 1 current daily smokers with current dysthymia (OR=2.13, 95% CI=1.23, 3.70) or minor depression (OR=1.53, 95% CI=1.07, 2.18) were more likely than smokers without the respective diagnosis to report continued smoking at Wave 2. Wave 1 former daily smokers with current dysthymia (OR=0.44, 95% CI=0.20, 0.96) and lifetime dysthymia (OR=0.37, 95% CI=0.15, 0.91) were less likely than those without the diagnosis to remain abstinent from smoking at Wave 2. The gender-by-diagnosis interactions were not significant, suggesting that the impact of dysthymia and minor depression on smoking behavior is similar among men and women. Current dysthymia and minor depression are associated with a greater likelihood of continued smoking; current and lifetime dysthymia are associated with a decreased likelihood of continued smoking abstinence. Weinberger A, Pilver C, Desai R, Mazure C, McKee S. The relationship of dysthymia, minor depression, and gender to changes in smoking for current and former smokers: Longitudinal evaluation in the U.S. population. Drug Alcohol Depend. 2013; 127(1-3): 170-176.

HIV, Age, and the Severity of Hepatitis C Virus-Related Liver Disease: A Cohort Study Persons with HIV infection have been reported to develop age-related diseases at younger ages than those without HIV. Whether this finding is related to HIV infection or failure to control for other risk factors is unknown. The objective of this study was to investigate whether persons with HIV infection develop hepatitis C virus (HCV)-related liver disease at younger ages than similar persons without HIV. The study design was a comparison of the severity of liver fibrosis by age among persons who have HCV with and without HIV followed concurrently in the same protocol. The study setting was an observational cohort from Baltimore, Maryland, participating in the ALIVE (AIDS Linked to the IntraVenous Experience) study. Participants included 1,176 current and former injection drug users with antibodies to HCV. Measurements included liver fibrosis assessed semiannually from 2006 to 2011 by elastography (FibroScan, Echosens, Paris, France) and using previously validated thresholds for clinically significant fibrosis and cirrhosis; concurrent assessment of medical history, alcohol and illicit drug use, HCV RNA levels, hepatitis B virus surface antigen level, body mass index, and (for those with HIV) CD4+ lymphocyte count and HIV RNA levels. Among 1,176 participants with antibodies to HCV, the median age was 49 years and 34% were coinfected with HIV and HCV. Participants contributed 5,634 valid liver fibrosis measurements. The prevalence of clinically significant fibrosis without cirrhosis (12.9% vs. 9.5%) and of cirrhosis (19.5% vs. 11.0%) was greater in persons coinfected with HIV and HCV than in those with only HCV ($P < 0.001$). Increasing age and HIV infection were independently associated with liver fibrosis, as were daily alcohol use, chronic hepatitis B virus infection, body mass index greater than 25 kg/m2, and greater plasma HCV RNA levels. When these factors were kept constant, persons with HIV had liver fibrosis measurements equal to those of persons without HIV,

who were, on average, 9.2 years older. A limitation of the study was that the process of liver fibrosis began before the study in most persons. The authors conclude that in this cohort, persons who have HCV with HIV have liver fibrosis stages similar to those without HIV who are nearly a decade older. Kirk G, Mehta S, Astemborski J, Galai N, Washington J, Higgins Y, Balagopal A, Thomas D. HIV, age, and the severity of Hepatitis C virus-related liver disease: A cohort study. Ann Intern Med. 2013; 1-11.

Relation Among HPA and HPG Neuroendocrine Systems, Transmissible Risk and Neighborhood Quality On Development Of Substance Use Disorder: Results Of A 10-Year Prospective Study Research has shown involvement of hormones of the hypothalamic pituitary adrenal (HPA) axis and hypothalamic pituitary gonadal (HPG) axis in the regulation of behaviors that contribute to SUD risk and its intergenerational transmission. Neighborhood environment has also been shown to relate to hormones of these two neuroendocrine systems and behaviors associated with SUD liability. Accordingly, it was hypothesized that (1) parental SUD severity and neighborhood quality correlate with activity of the HPG axis (testosterone level) and HPA axis (cortisol stability), and (2) transmissible risk during childhood mediates these hormone variables on development of SUD measured in adulthood. Transmissible risk for SUD measured by the transmissible liability index (TLI; Vanyukov et al., 2009) along with saliva cortisol, and plasma testosterone were prospectively measured in boys at ages 10-12 and 16. Neighborhood quality was measured using a composite score encompassing indicators of residential instability and economic disadvantage. SUD was assessed at age 22. Neither hormone variable cross-sectionally correlated with transmissible risk measured at ages 10-12 and 16. However, the TLI at age 10-12 predicted testosterone level and cortisol stability at age 16. Moreover, testosterone level, correlated with cortisol stability at age 16, predicted SUD at age 22. The authors conclude that HPA and HPG axes activity do not underlie variation in TLI, however, high transmissible risk in childhood predicts neuroendocrine system activity presaging development of SUD. Tarter R, Kirisci L, Kirillova G, Reynolds M, Gavaler J, Ridenour T, Horner M, Clark D, Vanyukov M. Relation aong HPA And HPG neuroendocrine systems, transmissible risk and neighborhood quality on development of substance use disorder: Results of a 10-year prospective study. Drug Alcohol Depend. 2013; 127(1-3): 226-231.

Sexual-Orientation Disparities in Cigarette Smoking in a Longitudinal Cohort Study of Adolescents Youths with a minority sexual orientation (i.e., gay, lesbian, bisexual, and mostly heterosexual) are at high risk for cigarette smoking. The authors examined sexual-orientation disparities in smoking during adolescence and emerging adulthood and investigated the role of age at first smoking in contributing to smoking disparities. They used data from the Growing Up Today Study, a large longitudinal cohort of adolescents followed from ages 12 to 24 years (N = 13,913). Self-administered questionnaires filled out annually or biennially assessed age at first smoking, current smoking, frequency of smoking, number of cigarettes smoked daily, and nicotine dependence. Proportional hazards survival analysis and repeated measures regression estimated sexual-orientation differences in smoking. Compared with completely heterosexuals, lesbian/gay, bisexual, and mostly heterosexual youths smoked their first cigarette at younger ages, were more likely to be current smokers, and had higher frequency of smoking. Among past-year smokers, sexual-minority females smoked more cigarettes daily and scored higher on nicotine dependence than completely heterosexual females. In some instances, gender and age modified relationships between sexual orientation and smoking, with relative risk accentuated in female sexual minorities and in sexual minorities during younger ages. Younger age of smoking onset contributed to elevated smoking in mostly heterosexuals and bisexuals, and to a lesser extent in lesbians, but not in gay

males. The authors conclude that sexual-orientation minorities are at greater risk for smoking during adolescence and emerging adulthood than heterosexuals. Disparities are larger in females and evident in early adolescence. Prevention and cessation efforts should target this population, preferably beginning in early adolescence. Corliss H, Wadler B, Jun H, Rosario M, Wypij D, Frazier A, Austin S. Sexual-orientation disparities in cigarette smoking in a longitudinal cohort study of adolescents. Nicotine Tob Res. 2013; 15(1): 213-222.

Quick Screen To Detect Current Substance Use Disorder In Adolescents and the Likelihood Of Future Disorder A brief screen requiring 3-4min administration time was developed to detect adolescents qualifying for current substance use disorder (SUD) and those who will subsequently manifest SUD by early adulthood. The revised Drug Use Screening Inventory (DUSI-R; Tarter, 1990) was administered to 329 boys on three occasions (ages 12-14, 15-17 and 18-19years of age). Principal components analysis yielded a core set of items to form three age-specific versions of the DUSI-R Quick Screen (DQS), consisting of the Substance Involvement Index and Problems Severity Index. Construct, concurrent and predictive validity of the DQS were in the good to excellent range. Sensitivity of the DQS at ages 12-14, 15-17 and 18-19 for detecting current SUD was 100%, 93% and 93%. The DQS at these ages predicted SUD by age 22 with 73%, 77% and 83% accuracy. Replication in another sample revealed sensitivity of 71% and 75% in 15-17 and 18-20year old males. The authors conclude that the true positive rate of detecting current and future SUD suggests that the DQS is an efficient screen for identifying youths requiring treatment or secondary prevention. Kirisci L, Reynolds M, Carver D, Tarter R. Quick screen to detect current substance use disorder in adolescents and the likelihood of future disorder. Drug Alcohol Depend. 2013; 128(1-2): 116-122.

Assessing Illicit Drug Use among Adults with Schizophrenia Accurate drug use assessment is vital to understanding the prevalence, course, treatment needs, and outcomes among individuals with schizophrenia because they are thought to remain at long-term risk for negative drug use outcomes, even in the absence of drug use disorder. This study evaluated self-report and biological measures for assessing illicit drug use in the Clinical Antipsychotic Trials of Intervention Effectiveness study (N=1460). Performance was good across assessment methods, but differed as a function of drug type, measure, and race. With the Structured Clinical Interview for DSM-III-R as the criterion, self-report evidenced greater concordance, accuracy and agreement overall, and for marijuana, cocaine, and stimulants specifically, than did urinalysis and hair assays, whereas biological measures outperformed self-report for detection of opiates. Performance of the biological measures was better when self-report was the criterion, but poorer for black compared white participants. Overall, findings suggest that self-report is able to garner accurate information regarding illicit drug use among adults with schizophrenia. Further work is needed to understand the differential performance of assessment approaches by drug type, overall and as a function of race, in this population. Van Dorn R, Desmarais S, Scott Young M, Sellers B, Swartz M. Assessing illicit drug use among adults with schizophrenia. Psychiatry Res. 2012; 200(2-3): 228-236.

Individual And Network Factors Associated With Prevalent Hepatitis C Infection Among Rural Appalachian Injection Drug Users The authors determined the factors associated with hepatitis C (HCV) infection among rural Appalachian drug users. This study included 394 injection drug users (IDUs) participating in a study of social networks and infectious disease risk in Appalachian Kentucky. Trained staff conducted HCV, HIV, and herpes simplex-2 virus (HSV-2) testing, and an interviewer-administered questionnaire measured self-reported risk behaviors and sociometric network characteristics. The prevalence of HCV infection was 54.6% among rural

IDUs. Lifetime factors independently associated with HCV infection included HSV-2, injecting for 5 or more years, posttraumatic stress disorder, injection of cocaine, and injection of prescription opioids. Recent (past-6-month) correlates of HCV infection included sharing of syringes (adjusted odds ratio = 2.24; 95% confidence interval = 1.32, 3.82) and greater levels of eigenvector centrality in the drug network. One factor emerged that was potentially unique to rural IDUs: the association between injection of prescription opioids and HCV infection. Therefore, preventing transition to injection, especially among prescription opioid users, may curb transmission, as will increased access to opioid maintenance treatment, novel treatments for cocaine dependence, and syringe exchange. Havens J, Lofwall M, Frost S, Oser C, Leukefeld C, Crosby R. Individual and network factors associated with prevalent Hepatitis C infection among rural Appalachian injection drug users. Am J Public Health. 2013; 103(1): e44-e52.

Drinking Consequence Types in the First College Semester Differentially Predict Drinking the Following Year The objectives of the present study were to examine the utility of distinguishing among negative consequence types when seeking to predict drinking later in college, to understand which consequences in particular were associated with future drinking, and to determine the direction of those associations. The authors also examined whether there were differences in the types of drinking outcomes (quantity, frequency, and binge) predicted by unique consequences. Finally, they tested whether the link between consequences and future drinking was different for men versus for women. Incoming first year college students (n=997; 65% female) completed an online assessment in September of the first college year, and again at the same time the following year. Results of structural equation model tests offered support for the utility of distinguishing among different consequence types, as specific consequences experienced during the first semester of college were associated differently with drinking at the beginning of the second school year. Gender differences also were observed. For both men and women, social consequences were associated with increases in drinking over time. Blackout drinking also evidenced prospective prediction, but differentially for men and women. For men, these consequences were associated with later increases in drinking, whereas for women, they were associated with a diminution in drinking the next year. For men, only consequences associated with self-care (impairment in physical activity, physical appearance, less time to pursue recreation) predicted decreases in drinking at Year 2. Prediction was generally similar across drinking outcomes. Results suggest that whether negative consequences result in downward titration, escalation, or no change at all in later drinking depends on the type of consequence experienced, and who experiences it. Read J, Wardell J, Bachrach R. Drinking consequence types in the first college semester differentially predict drinking the following year. Addict Behav. 2013; 38(1): 1464-1471.

Adversity And Syndemic Production Among Men Participating In The Multicenter AIDS Cohort Study: A Life-Course Approach The authors tested a theory of syndemic production among men who have sex with men (MSM) using data from a large cohort study. Participants were 1,551 men from the Multicenter AIDS Cohort Study enrolled at 4 study sites: Baltimore, Maryland-Washington, DC; Chicago, Illinois; Los Angeles, California; and Pittsburgh, Pennsylvania. Participants who attended semiannual visits from April 1, 2008, to March 31, 2009, completed an additional survey that captured data about events throughout their life course thought to be related to syndemic production. Using multivariate analysis, we found that the majority of life-course predictor variables (e.g., victimization, internalized homophobia) were significantly associated with both the syndemic condition and the component psychosocial health outcomes (depressive symptoms, stress, stimulant use, sexual compulsivity, intimate partner violence). A nested negative binomial analysis showed that the overall life course significantly explained variability in the

syndemic outcomes (Ç(2) = 247.94; P < .001; df = 22). The authors identified life-course events and conditions related to syndemic production that may help to inform innovative interventions that will effectively disentangle interconnecting health problems and promote health among MSM. Herrick A, Lim S, Plankey M, Chmiel J, Guadamuz T, Kao U, Shoptaw S, Carrico A, Ostrow D, Stall R. Adversity and syndemic production among men participating in the Multicenter AIDS Cohort Study: A life-course approach. Am J Public Health. 2013; 103(1): 79-85.

HIV Incidence Determination In The United States: A Multiassay Approach Accurate testing algorithms are needed for estimating human immunodeficiency virus (HIV) incidence from cross-sectional surveys. The authors developed a multiassay algorithm (MAA) for HIV incidence that includes the BED capture enzyme immunoassay (BED-CEIA), an antibody avidity assay, HIV load, and CD4(+) T-cell count. They analyzed 1,782 samples from 709 individuals in the United States who had a known duration of HIV infection (range, 0 to >8 years). Logistic regression with cubic splines was used to compare the performance of the MAA to the BED-CEIA and to determine the window period of the MAA. They compared the annual incidence estimated with the MAA to the annual incidence based on HIV seroconversion in a longitudinal cohort. The MAA had a window period of 141 days (95% confidence interval [CI], 94-150) and a very low false-recent misclassification rate (only 0.4% of 1474 samples from subjects infected for >1 year were misclassified as indicative of recent infection). In a cohort study, annual incidence based on HIV seroconversion was 1.04% (95% CI, .70%-1.55%). The incidence estimate obtained using the MAA was essentially identical: 0.97% (95% CI, .51%-1.71%). The authors conclude that the MAA is as sensitive for detecting recent HIV infection as the BED-CEIA and has a very low rate of false-recent misclassification. It provides a powerful tool for cross-sectional HIV incidence determination. Laeyendecker O, Brookmeyer R, Cousins M, Mullis C, Konikoff J, Donnell D, Celum C, Buchbinder S, Seage G, Kirk G, Mehta S, Astemborski J, Jacobson L, Margolick J, Brown J, Quinn T, Eshleman S. HIV incidence determination in the United States: A multiassay approach. J Infect Dis. 2013; 207(2): 232-239.

Risk Behaviors Among HIV-Positive Gay and Bisexual Men At Party-Oriented Vacations This study examined substance use (intended and actual), unprotected sex, and HIV disclosure practices (disclosure and questioning) among HIV-positive men who have sex with men (MSM) at two party-oriented vacations, where substance use and sexual risk may be heightened. A random sample of 489 MSM attending one of two party-oriented vacations participated in PartyIntents, a short-term longitudinal survey. Nearly half (47%) completed a follow-up assessment at the event or online for up to 2 weeks after the event. The authors examined rates of baseline intentions to use substances, actual substance use, and unprotected intercourse among HIV-positive men in attendance. Rates among HIV-negative men were estimated for comparison. Multiple logistic regression was used to assess the impact of illegal drug use and HIV status on unprotected anal intercourse (UAI). HIV-positive attendees (17%) were significantly more likely than HIV-negative attendees to use nitrite inhalants (or "poppers") (24.3% vs. 10.7%). HIV-positive attendees were also significantly more likely to have insertive UAI (64.3% vs. 34.1%) and receptive UAI (68.8% vs. 22.2%). Multivariate models showed associations between HIV status and illegal drug use with UAI (for HIV status, odds ratio [OR] = 4.5, p = .001; for any illegal drug use, OR = 16.4, p < .001). There was no evidence that the influence of drug use moderated risk by HIV status. Rates of HIV disclosure and questioning did not differ by HIV status. The authors conclude that HIV-positive men attending these events engaged in higher rates of illegal drug use and sexual risk than HIV-negative men. Prevention campaigns targeting MSM at high-risk events should include messages geared toward

HIV-positive men. Fisher M, Ramchand R, Bana S, Iguchi M. Risk behaviors among HIV-positive gay and bisexual men at party-oriented vacations. J Stud Alcohol Drugs. 2013; 74(1): 158-167.

The Impact Of Social, Structural and Physical Environmental Factors On Transitions Into Employment Among People Who Inject Drugs Despite growing awareness of the importance of context for the health of people who use drugs, studies examining labour market outcomes have rarely considered the role that physical, social and structural factors play in shaping labour market participation among drug users. Using discrete time event history analyses, the authors assessed associations between high-intensity substance use, individual drug use-related risk and features of inner-city drug use scenes with transitions into regular employment. Data were derived from a community-recruited cohort of people who inject drugs in Vancouver, Canada (n = 1579) spanning the period of May 1996-May 2005. Results demonstrate that systematic socio-demographic differences in labour market outcomes in this context generally correspond to dimensions of demographic disadvantage. Additionally, in initial analyses, high-intensity substance use is negatively associated with transitions into employment. However, this negative association loses significance when indicators measuring exposure to physical, social and structural features of the broader risk environment are considered. These findings indicate that interventions designed to improve employment outcomes among drug users should address these social, structural and physical components of the risk environment as well as promote the cessation of drug use. Richardson L, Wood E, Kerr T. The impact of social, structural, and physical environmental factors on transitions into employment among people who inject drugs. Soc Sci Med. 2013; 76(1): 126-133.

Housing Status And The Health Of People Living With HIV/AIDS Individuals who are homeless or living in marginal conditions have an elevated burden of infection with HIV. Existing research suggests the HIV/AIDS pandemic in resource-rich settings is increasingly concentrated among members of vulnerable and marginalized populations, including homeless/marginally-housed individuals, who have yet to benefit fully from recent advances in highly-active antiretroviral therapy (HAART). The authors reviewed the scientific evidence investigating the relationships between inferior housing and the health status, HAART access and adherence and HIV treatment outcomes of people living with HIV/AIDS (PLWHA.) Studies indicate being homeless/marginally-housed is common among PLWHA and associated with poorer levels of HAART access and sub-optimal treatment outcomes. Among homeless/marginally-housed PLWHA, determinants of poorer HAART access/adherence or treatment outcomes include depression, illicit drug use, and medication insurance status. Future research should consider possible social- and structural-level determinants of HAART access and HV treatment outcomes that have been shown to increase vulnerability to HIV infection among homeless/marginally-housed individuals. As evidence indicates homeless/marginally-housed PLWHA with adequate levels of adherence can benefit from HAART at similar rates to housed PLWHA, and given the individual and community benefits of expanding HAART use, interventions to identify HIV-seropositive homeless/marginally-housed individuals, and engage them in HIV care including comprehensive support for HAART adherence are urgently needed. Milloy M, Marshall B, Montaner J, Wood E. Housing status and the health of people living with HIV/AIDS. Curr HIV/AIDS Rep. 2012; 9(4): 364-374.

Mood and Smoking Behavior: The Role of Expectancy Accessibility and Gender Little is known about overall or gender-specific factors that may influence the relationship between negative affect and smoking behavior such as smoking expectancies. This paper presents a secondary analysis from a laboratory studying gender differences in smoking behavior following a musical

mood induction [Weinberger AH, McKee SA. Gender differences in smoking following an implicit mood induction. Nicotine & Tobacco Research 2012; 14(5): 621-625]. The current analyses examine the role of expectancies (endorsement and accessibility) in the relationship of gender, affect, and smoking. Ninety adult smokers (50% female) were randomly assigned to a negative mood induction, positive mood induction, or neutral condition while completing a single laboratory session. Expectancy endorsement, expectancy accessibility, affect, and smoking topography were assessed following the mood induction. Female smokers with faster accessibility of negative reinforcement expectancies smoked more cigarettes, had longer puff durations, and had shorter inter-puff intervals. Women with faster expectancy accessibility were also more likely to endorse negative reinforcement smoking expectancies. This study was the first to demonstrate links among gender, mood, and accessibility of smoking-related beliefs. Information about the role of expectancy accessibility in smoking behavior can lead to both a better understanding of gender-specific mechanisms of smoking behavior and new directions for smoking treatment development. Weinberger A, McKee S. Mood and smoking behavior: The role of expectancy accessibility and gender. Addict Behav. 2012; 37(12): 1349-1352.

Genome-Wide Association Study Of Spontaneous Resolution Of Hepatitis C Virus Infection: Data From Multiple Cohorts Hepatitis C virus (HCV) infections occur worldwide and either spontaneously resolve or persist and markedly increase the person's lifetime risk for cirrhosis and hepatocellular carcinoma. Although HCV persistence occurs more often in persons of African ancestry and persons with genetic variants near interleukin-28B (IL-28B), the genetic basis is not well-understood. The objective of this study was to evaluate the host genetic basis for spontaneous resolution of HCV infection. These were 2-stage, genome-wide association studies. The settings were 13 international multicenter study sites. Patients comprised 919 persons with serum HCV antibodies but no HCV RNA (spontaneous resolution) and 1,482 persons with serum HCV antibodies and HCV RNA (persistence). Measurements obtained were frequencies of 792,721 single nucleotide polymorphisms (SNPs). Differences in allele frequencies between persons with spontaneous resolution and persistence were identified on chromosomes 19q13.13 and 6p21.32. On chromosome 19, allele frequency differences localized near IL-28B and included rs12979860 (overall per-allele OR, 0.45; P = 2.17 × 10-30) and 10 additional SNPs spanning 55 000 base pairs. On chromosome 6, allele frequency differences localized near genes for HLA class II and included rs4273729 (overall per-allele OR, 0.59; P = 1.71 × 10-16) near DQB1*03:01 and an additional 116 SNPs spanning 1 090 000 base pairs. The associations in chromosomes 19 and 6 were independent and additive and explain an estimated 14.9% (95% CI, 8.5% to 22.6%) and 15.8% (CI, 4.4% to 31.0%) of the viiation in HCV resolution in persons of European and African ancestry, respectively. Replication of the chromosome 6 SNP, rs4272729, in an additional 745 persons confirmed the findings (P = 0.015). A limitation of this research was that epigenetic effects were not studied. The authors conclude that IL-28B and HLA class II are independently associated with spontaneous resolution of HCV infection, and SNPs marking IL-28B and DQB1*03:01 may explain approximately 15% of spontaneous resolution of HCV infection. Duggal P, Thio C, Wojcik G, Goedert J, Mangia A, Latanich R, Kim A, Lauer G, Chung R, Peters M, Kirk G, Mehta S, Cox A, Khakoo S, Alric L, Cramp M, Donfield S, Edlin B, Tobler L, Busch M, Alexander G, Rosen H, Gao X, Abdel-Hamid M, Apps R, Carrington M, Thomas D. Genome-wide association study of spontaneous resolution of Hepatitis C Virus infection: Data from multiple cohorts. Ann Intern Med. 2013; 158(4): 235-245.

PREVENTION RESEARCH

Longitudinal Effects of Universal Preventive Intervention on Prescription Drug Misuse: Three Randomized Controlled Trials With Late Adolescents and Young Adults The authors examined long-term prescription drug misuse outcomes in 3 randomized controlled trials evaluating brief universal preventive interventions conducted during middle school. Methods. In 3 studies, they tested the Iowa Strengthening Families Program (ISFP); evaluated a revised ISFP, the Strengthening Families Program: For Parents and Youth 10-14 plus the school-based Life Skills Training (SFP 10-14 + LST); and examined the SFP 10-14 plus 1 of 3 school-based interventions. Self-reported outcomes were prescription opioid misuse (POM) and lifetime prescription drug misuse overall (PDMO). Results. In study 1, ISFP showed significant effects on POM and PDMO, relative reduction rates (RRRs; age 25 years) of 65%, and comparable benefits for higher- and lower-risk subgroups. In study 2, SFP 10-14 + LST showed significant or marginally significant effects on POM and PDMO across all ages (21, 22, and 25 years); higher-risk participants showed stronger effects (RRRs = 32%-79%). In study 3, the authors found significant results for POM and PDMO (12th grade RRRs = 20%-21%); higher-risk and lower-risk participants showed comparable outcomes. The authors conclude that brief universal interventions have potential for public health impact by reducing prescription drug misuse among adolescents and young adults. Spoth R, Trudeau L, Shin C, Ralston E, Redmond C, Greenberg M, Feinberg M. Longitudinal effects of universal preventive intervention on prescription drug misuse: three randomized controlled trials with late adolescents and young adults. Am J Public Health.Published online ahead of print February 14, 2013: e1-e8.

Effect of a Paraprofessional Home-Visiting Intervention on American Indian Teen Mothers' and Infants' Behavioral Risks: a Randomized Controlled Trial The authors sought to examine the effectiveness of Family Spirit, a paraprofessional-delivered, home-visiting pregnancy and early childhood intervention in improving American Indian teen mothers' parenting outcomes and mothers' and children's emotional and behavioral functioning 12 months postpartum. Pregnant American Indian teens(N=322) from four southwestern tribal reservation communities were randomly assigned in equal numbers to the Family Spirit intervention plus optimized standard care or to optimized standard care alone. Parent and child emotional and behavioral outcome data were collected at baseline and at 2, 6, and 12 months postpartum using self-reports, interviews, and observational measures. At 12 months postpartum, mothers in the intervention group had significantly greater parenting knowledge parenting self-efficacy, and home safety attitudes and fewer externalizing behaviors, and their children had fewer externalizing problems. In a subsample of mothers with any lifetime substance use at baseline (N=285; 88.5%), children in the intervention group had fewer externalizing and dysregulation problems than those in the standard care group, and fewer scored in the clinically at risk range (10th percentile) for externalizing and internalizing problems. No between-group differences were observed for outcomes measured by the Home Observation for Measurement of the Environment scale. Outcomes 12 months postpartum suggest that the Family Spirit intervention improves parenting and infant outcomes that predict lower lifetime behavioral and drug use risk for participating teen mothers and children. Barlow A, Mullany B, Neault N, Compton S, Carter A, Hastings R, Billy T, Coho-Mescal V, Lorenzo S, Walkup J. Effect of a paraprofessional home-visiting intervention on American Indian teen mothers' and infants' behavioral risks: A randomized controlled trial. Am J Psychiatry. 2013; 170(1): 83-93.

Differential Susceptibility to Prevention: GABAergic, Dopaminergic, and Multilocus Effects Randomized prevention trials provide a unique opportunity to test hypotheses about the interaction of genetic predispositions with contextual processes to create variations in phenotypes over time. Using two longitudinal, randomized prevention trials, molecular genetics, and alcohol use outcome data were gathered from more than 900 youths to determine whether prevention program participation would, across 2 years, moderate genetic risk for increased alcohol use conferred by the dopaminergic and GABAergic systems. The authors found that (a) variance in dopaminergic (DRD2, DRD4, ANKK1) and GABAergic (GABRG1, GABRA2) genes forecast increases in alcohol use across 2 years, and (b) youths at genetic risk who were assigned to the control condition displayed greater increases in alcohol use across 2 years than did youths at genetic risk who were assigned to the prevention condition or youths without genetic risk who were assigned to either condition. This study is unique in combining data from two large prevention trials to test hypotheses regarding genetic main effects and gene × prevention interactions. Focusing on gene systems purported to confer risk for alcohol use and abuse, the study demonstrated that participation in efficacious prevention programs can moderate genetic risk. The results also support the differential susceptibility hypothesis that some youths, for genetic reasons, are more susceptible than others to both positive and negative contextual influences. Brody G, Chen Y, Beach S. Differential susceptibility to prevention: Gabaergic, dopaminergic, and multilocus effects. J Child Psychol Psychiatry. 2013; doi: 10.1111/jcpp.12042: 1-9.

PROSPER Community-University Partnership Delivery System Effects On Substance Misuse Through 6 1/2 Years Past Baseline From A Cluster Randomized Controlled Intervention Trial The objective of this study was to examine the effects of a delivery system for evidence-based preventive interventions through 12th grade, 6.5years past baseline. A cohort sequential design included 28 public school districts randomly assigned to the partnership delivery system or usual-programming conditions. At baseline, 11,960 students participated. Partnerships supported community teams that implemented a family-focused intervention in 6th grade and a school-based intervention in 7th grade. Outcome measures included lifetime, current misuse, and frequencies of misuse, for a range of substances. Intent-to-treat, multilevel analyses of covariance of point-in-time misuse and analyses of growth in misuse were conducted. Results showed significantly lower substance misuse in the intervention group at one or both time points for most outcomes, with relative reduction rates of up to 31.4%. There was significantly slower growth in misuse in the intervention group for 8 of the 10 outcomes. In addition, risk moderation results indicated that there were significantly greater intervention benefits for higher- versus lower-risk youth, for the misuse of 6 of the 10 substances at 11th grade, illicit substances at 12th grade, and growth in the misuse of illicit substances. The authors conclude that partnership-based delivery systems for brief universal interventions have potential for public health impact by reducing substance misuse among youth, particularly higher-risk youth. Spoth R, Redmond C, Shin C, Greenberg M, Feinberg M, Schainker L. PROSPER community-university partnership delivery system effects on substance misuse through 6 1/2years past baseline from a cluster randomized controlled intervention trial. Prev Med. 2013; 56(3-4): 190-196.

Differential Sensitivity to Prevention Programming: A Dopaminergic Polymorphism-Enhanced Prevention Effect on Protective Parenting and Adolescent Substance Use The purpose of this study was to investigate a genetic moderation effect of dopamine receptor-4 gene (DRD4) alleles that have 7 or more repeats on the efficacy of a preventive intervention to deter rural African American adolescents' substance use. Adolescents (N = 502, M age = 16 years) were assigned randomly to the Strong African American Families-Teen (SAAF-T) program or to a

control condition and were followed for 22 months. Adolescents provided data on substance use, and both adolescents and their primary caregivers provided data on intervention-targeted protective parenting practices. Male adolescents who carried at least one allele of DRD4 with 7 or more repeats who were assigned to the control condition evinced more substance use across 22 months than did (a) carriers of at least one allele of DRD4 with 7 or more repeats who were assigned to SAAF-T or (b) adolescents assigned to either condition who carried two alleles of DRD4 with 6 or fewer repeats. These findings were mediated by DRD4 × SAAF-T interaction effects on increases in intervention-targeted protective parenting practices, a mediated moderation effect. The results imply that prevention effects on health-relevant outcomes for genetically susceptible individuals, such as carriers of at least one allele of DRD4 with 7 or more repeats, may be underestimated. (PsycINFO Database Record (c) 2013 APA, all rights reserved). Brody G, Chen Y, Beach S, Kogan S, Yu T, Diclemente R, Wingood G, Windle M, Philibert R. Differential sensitivity to prevention programming: A dopaminergic polymorphism-enhanced prevention effect on protective parenting and adolescent substance use. Health Psychol. 2013; doi: 10.1037/a0031253: 1-10.

Depressive Symptom Trajectories Among Girls in the Juvenile Justice System: 24-month Outcomes of an RCT of Multidimensional Treatment Foster Care Youth depression is a significant and growing international public health problem. Youth who engage in high levels of delinquency are at particularly high risk for developing problems with depression. The present study examined the impact of a behavioral intervention designed to reduce delinquency (Multidimensional Treatment Foster Care; MTFC) compared to a group care intervention (GC; i.e., services as usual) on trajectories of depressive symptoms among adolescent girls in the juvenile justice system. MTFC has documented effects on preventing girls' recidivism, but its effects on preventing the normative rise in girls' depressive symptoms across adolescence have not been examined. This indicated prevention sample included 166 girls (13-17 years at T1) who had at least one criminal referral in the past 12 months and who were mandated to out-of-home care; girls were randomized to MTFC or GC. Intent-to-treat analyses examined the main effects of MTFC on depression symptoms and clinical cut-offs, and whether benefits were greatest for girls most at risk. Depressive symptom trajectories were specified in hierarchical linear growth models over a 2 year period using five waves of data at 6 month intervals. Depression clinical cut-off scores were specified as nonlinear probability growth models. Results showed significantly greater rates of deceleration for girls in MTFC versus GC for depressive symptoms and for clinical cut-off scores. The MTFC intervention also showed greater benefits for girls with higher levels of initial depressive symptoms. Possible mechanisms of effect are discussed, given MTFC's effectiveness on targeted and nontargeted outcomes. Harold G, Kerr D, Van Ryzin M, Degarmo D, Rhoades K, Leve L. Depressive symptom trajectories among girls in the juvenile justice system: 24-month outcomes of an RCT of multidimensional treatment foster care. Prev Sci. 2013.

Social-Information-Processing Patterns Mediate the Impact of Preventive Intervention on Adolescent Antisocial Behavior In the study reported here, the authors tested the hypothesis that the Fast Track preventive intervention's positive impact on antisocial behavior in adolescence is mediated by its impact on social-cognitive processes during elementary school. Fast Track is the largest and longest federally funded preventive intervention trial for children showing aggressive behavior at an early age. Participants were 891 high-risk kindergarten children (69% male, 31% female; 49% ethnic minority, 51% ethnic majority) who were randomly assigned to an intervention or a control group by school cluster. Multiyear intervention addressed social-cognitive processes through social-skill training groups, parent groups, classroom curricula, peer coaching, and tutoring. Assigning children to the intervention decreased their mean antisocial-behavior score after Grade 9

by 0.16 standardized units ($p < .01$). Structural equation models indicated that 27% of the intervention's impact on antisocial behavior was mediated by its impact on three social-cognitive processes: reducing hostile-attribution biases, increasing competent response generation to social problems, and devaluing aggression. These findings support a model of antisocial behavioral development mediated by social-cognitive processes, and they guide prevention planners to focus on these processes. Dodge K, Godwin J, Godwin J. Social-information-processing patterns mediate the impact of preventive intervention on adolescent antisocial behavior. Psychol Sci. 2013.

Examining a Home Environmental Strategy to Reduce Availability of Legal Products that Can Be Misused by Youth This article presents results from a study of a home environmental strategy (HES) designed to reduce availability of harmful legal products (HLPs) in the home that can be used by youth to get high. HLPs include inhalants, prescription and nonprescription drugs, and household products that can be ingested to get high. Availability is one of the most consistent predictors of substance use among youth. Parents of 5th- to 7th-grade students in four Alaskan communities participated in telephone interviews as part of a larger study of a multicomponent community prevention model (CPM) that included a HES. The strategy was designed to encourage parents to reduce availability of HLPs by removing them from the home, and by locking up and monitoring the supplies of HLPs in the home. Data from 402 parents at Wave 1 and 371 parents at Wave 2 were analyzed using hierarchical non-Linear modeling (HNLM). Results show there was a significant decrease in HLPs in the home from Wave 1 to Wave 2, mostly inhalants and prescription and nonprescription drugs. Parents also reported a significant increase in locking up prescription and nonprescription drugs in the home. Parents' direct exposure to the HES was marginally associated with the change over time in HLP availability in the home. Indirect exposure through others and media was not associated with this change. Study lessons learned and conclusions are highlighted. Collins D, Johnson K, Shamblen S. Examining a home environmental strategy to reduce availability of legal products that can be misused by youth. Subst Use Misuse. 2012; 47(12): 1339-1348.

Siblings Are Special: Initial Test of a New Approach for Preventing Youth Behavior Problems A growing body of research documents the significance of siblings and sibling relationships for development, mental health, and behavioral risk across childhood and adolescence. Nonetheless, few well-designed efforts have been undertaken to promote positive and reduce negative youth outcomes by enhancing sibling relationships. Based on a theoretical model of sibling influences, the authors conducted a randomized trial of Siblings Are Special (SIBS), a group-format afterschool program for fifth graders with a younger sibling in second through fourth grades, which entailed 12 weekly afterschool sessions and three Family Nights. The authors tested program efficacy with a pre- and post-test design with 174 families randomly assigned to condition. In home visits at both time points, they collected data via parent questionnaires, child interviews, and observer-rated videotaped interactions and teachers rated children's behavior at school. The program enhanced positive sibling relationships, appropriate strategies for parenting siblings, and child self-control, social competence, and academic performance; program exposure was also associated with reduced maternal depression and child internalizing problems. Results were robust across the sample, not qualified by sibling gender, age, family demographics, or baseline risk. No effects were found for sibling conflict, collusion, or child externalizing problems; the authors will examine follow-up data to determine if short-term impacts lead to reduced negative behaviors over time. They concluded that the breadth of the SIBS program's impact is consistent with research suggesting that siblings are an important influence on development and adjustment and supports our argument that a sibling focus should be incorporated into youth and family-oriented prevention programs. Feinberg M,

Solmeyer A, Hostetler M, Sakuma K, Jones D, McHale S. Siblings Are Special: Initial test of a new approach for preventing youth behavior problems. J Adolesc Health. 2012; doi:10.1016/ j.jadohealth.2012.10.004 1-8.

An Evaluation of Immediate Outcomes and Fidelity of a Drug Abuse Prevention Program in Continuation High Schools: Project Towards No Drug Abuse (TND) The present study provides an implementation fidelity, process, and immediate outcomes evaluation of Project Towards No Drug Abuse (TND), a drug prevention program targeting continuation high school youth (n=1426) at risk for drug abuse. A total of 24 schools participated in three randomized conditions: TND Only, TND and motivational interviewing follow-up, and no treatment control. Fidelity was high: across program schools the curriculum was implemented as intended and was received favorably by students. Relative to controls, intervention conditions produced effects on hypothesized mediators, including greater gains in program related knowledge, greater reductions in drug use intentions, and positive changes in motivation. However, few generalizations to attitudes and intentions regarding risky sexual behavior were found. The pattern of results suggests that the experimental manipulations worked as intended. Lisha N, Sun P, Rohrbach L, Spruijt-Metz D, Unger J, Sussman S. An evaluation of immediate outcomes and fidelity of a drug abuse prevention program in continuation high schools: Project Towards No Drug Abuse (TND). J Drug Educ. 2012; 42(1): 33-57.

Prevention Education Effects On Fundamental Memory Processes This study evaluated effects of a key session from a nationally recognized drug abuse prevention program on basic memory processes in 211 high-risk youth in Southern California. In a randomized, between-subject design, the authors manipulated assignment to a Myth and Denial program session and the time of assessment (immediate vs. 1-week delay). The authors examined program decay effects on memory accessibility and judgment errors. Those participants exposed to the program session generated more myths and facts from the program than those in the control group, suggesting that even a single program session influenced students' memory for program information and this was retained at least 1 week and detectable with indirect tests of memory accessibility. However, consistent with basic research perspectives, participants in the program-delayed assessment group erroneously generated more fact-related information from the session to the prompt "It is a myth that_____" than the participants in the program immediate assessment group; that is, they retained more facts as myths. These types of program effects, anticipated by basic memory theory, were not detected with a traditional judgment task in the present sample. The results suggest that basic science approaches offer a novel way of conceptually recasting prevention effects to more completely understand how these effects may operate. Implications for program evaluation and conceptualization are discussed. Ames S, Krank M, Grenard J, Sussman S, Stacy A. Prevention education effects on fundamental memory processes. Eval Health Prof. 2012; 35(4): 416-439.

Enhancing Sibling Relationships To Prevent Adolescent Problem Behaviors: Theory, Design And Feasibility of Siblings Are Special Siblings play a significant but neglected role in family socialization dynamics, and focusing on the sibling relationship is a non-stigmatizing point of entry into the family for prevention programming. Siblings are Special (SAS) was designed as a universal program that targets both sibling relationship and parenting mediating processes in middle childhood to prevent behavior problems in adolescence. The authors describe the theoretical framework underlying SAS, the SAS curriculum, and the feasibility of the program based on a study of 128 middle-childhood aged sibling dyads. Data on the quality of program implementation, program fidelity, siblings' engagement, and ratings of impact indicated the SAS program was

acceptable to families and schools, that the curriculum could be implemented with high fidelity, that siblings and parents participated at high levels and were highly engaged, and that, from the perspective of group leaders, school administrators and parents, the program had a positive impact on the siblings. Feinberg M, Sakuma K, Hostetler M, McHale S. Enhancing sibling relationships to prevent adolescent problem behaviors: Theory, design and feasibility of Siblings Are Special. Eval Program Plann. 2013; 36(1): 97-106.

Cumulative Socioeconomic Status Risk, Allostatic Load, and Adjustment: A Prospective Latent Profile Analysis With Contextual and Genetic Protective Factors The health disparities literature has identified a common pattern among middle-aged African Americans that includes high rates of chronic disease along with low rates of psychiatric disorders despite exposure to high levels of cumulative socioeconomic status (SES) risk. The current study was designed to test hypotheses about the developmental precursors to this pattern. Hypotheses were tested with a representative sample of 443 African American youths living in the rural South. Cumulative SES risk and protective processes were assessed at ages 11-13 years; psychological adjustment was assessed at ages 14-18 years; genotyping at the 5-HTTLPR was conducted at age 16 years; and allostatic load (AL) was assessed at age 19 years. A latent profile analysis identified 5 profiles that evinced distinct patterns of SES risk, AL, and psychological adjustment, with 2 relatively large profiles designated as focal profiles: a physical health vulnerability profile characterized by high SES risk/high AL/low adjustment problems, and a resilient profile characterized by high SES risk/low AL/low adjustment problems. The physical health vulnerability profile mirrored the pattern found in the adult health disparities literature. Multinomial logistic regression analyses indicated that carrying an s allele at the 5-HTTLPR and receiving less peer support distinguished the physical health vulnerability profile from the resilient profile. Protective parenting and planful self-regulation distinguished both focal profiles from the other 3 profiles. The results suggest the public health importance of preventive interventions that enhance coping and reduce the effects of stress across childhood and adolescence. (PsycINFO Database Record (c) 2012 APA, all rights reserved). Brody G, Yu T, Chen Y, Kogan S, Evans G, Beach S, Windle M, Simons R, Gerrard M, Gibbons F, Philibert R. Cumulative socioeconomic status risk, allostatic load, and adjustment: A prospective latent profile analysis with contextual and genetic protective factors. Dev Psychol. 2012; doi: 10.1037/a0028847: 1-15.

Demethylation of the Aryl Hydrocarbon Receptor Repressor as a Biomarker for Nascent Smokers Epigenetic modifications to peripheral white blood cell DNA occur in response to a wide variety of exposures. In prior work, the authors and others have shown that broad changes in DNA methylation, particularly at the aryl hydrocarbon receptor repressor (AHRR) locus, occur in samples from subjects with long histories of smoking. However, given the large number of epigenetic changes that occur in response to prolonged smoking, the primacy of the response at AHRR and the sensitivity of these changes to low levels of smoking are not known. Therefore, the authors examined the association of smoking to genome lymphocyte DNA methylation status in a representative sample of 399 African American youths living in the rural South that includes 72 subjects with less than one half-pack year of exposure. Consistent with the authors' prior findings, they found a stepwise effect of smoking on DNA methylation among youth with relatively brief exposure histories at a CpG residue in AHRR (cg05575921) (FDR corrected p values; 3×10 (-7) and 0.09 in the male and female samples, respectively) that was identified in previous studies and at which the effects of smoking were significant, even in those subjects with less than one half pack year exposure. The authors conclude that AHRR demethylation at cg05575921 in peripheral cells may serve as an early, sensitive biomarker for even low levels of exposure to tobacco smoke,

providing a non-self-report alternative for nascent exposure to tobacco smoke. They also suggest that the AHRR/AHR pathway may be functional in the response of peripheral white blood cells to tobacco smoke exposure. Philibert R, Beach S, Brody G. Demethylation of the Aryl hydrocarbon receptor repressor as a biomarker for nascent smokers. Epigenetics. 2012; 7(11): 1331-1338.

Perceptions of HIV Risk Among Internet-using, HIV-negative Barebacking Men The current study examines the risk perceptions of HIV-negative men who have sex with men (MSM) who use the Internet to seek unprotected sex. The research questions include the following: How great do these men perceive their HIV risk to be? Are their perceptions based on HIV knowledge or related to their risk behaviors? What factors are associated with greater/lesser perceived risk? Results revealed that more than half of the men believed that they had no or only a slight chance of contracting HIV. Risk perceptions were not related to HIV knowledge or to involvement in HIV risk practices. Four factors were identified as being associated with greater perception of HIV risk: self-identity as a sexual "bottom," having sex while high, greater use of bareback-focused websites, and younger age. Internet-using HIV-negative men who have sex with men tend to underestimate their risk for acquiring HIV, and interventions need to help them accurately assess their risk. Klein H, Tilley D. Perceptions of HIV risk among internet-using, HIV-Negative Barebacking Men. Am J Mens Health. 2012; 6(4): 280-293.

A Comparison of HIV Risk Practices Among Unprotected Sex-seeking Older and Younger Men Who Have Sex with Other Men In recent years, much attention has been devoted to understanding the HIV risk behaviors of younger men who have sex with men (MSM). Recent data suggest that HIV is becoming an increasing problem for older adults, but little attention has been devoted to understanding their HIV risk behaviors or the factors that underlie their risk taking. This study provides a comparison of these issues among younger and older MSM. The data come from a subset of younger (ages 18-39, n = 113) and older (ages 50+, n = 109) men participating in a national study of 332 men who use the Internet to find other men for unprotected sex. Men were sampled randomly from 16 websites. Data were collected via telephone interviews conducted in 2008 and 2009. Younger and older men reported comparable involvement in HIV risk, including involvement in unprotected sex, proportion of sex acts involving internal ejaculation, number of times having anonymous sex, and number of times having multiple-partner sex. Generally speaking, the factors underlying the risk practices of younger and older men were quite different (e.g. self-esteem and condom use self-efficacy for younger men, versus HIV serostatus and depression for older men). The authors conclude that older MSM using the Internet to find partners for unprotected sex engage in high rates of behaviors that place them at risk for contracting or transmitting HIV. They were just as likely as their younger counterparts to practice these behaviors. The factors "fueling" involvement in risk generally differ for older and younger men, thereby warranting the development of age-specific HIV interventions that can take into account the unique life circumstances and needs of older MSM. Klein H. A comparison of HIV risk practices among unprotected sex-seeking older and younger men who have sex with other men. Aging Male. 2012; 15(3): 124-133.

Substance Use Progression From Adolescence To Early Adulthood: Effortful Control In The Context Of Friendship Influence And Early-Onset Use In a sample of 998 ethnically diverse adolescents, a multi-agent, multi-method approach to the measurement of adolescent effortful control, adolescent substance use, and friendship influence was used to predict escalations to early-adult tobacco, alcohol, and marijuana use by ages 22-23. Structural equation modeling revealed that adolescent substance use and friends' substance use tended to be highly correlated and together were

robust predictors of a problematic pattern of usage for all substances in early adulthood. In addition, the adolescent effortful control construct directly predicted progressions to problematic use of tobacco and marijuana, but not for alcohol. In the alcohol model, effortful control interacted with the construct of substance use lifestyle (based on adolescent alcohol use and friends' substance use) when predicting problematic alcohol use in early adulthood. Results held when comparing across genders and across ethnic groups. These findings emphasize the importance of addressing adolescent self-regulation in interventions designed to treat and prevent early-adult substance abuse. Piehler T, Véronneau M, Dishion T. Substance use progression from adolescence to early adulthood: Effortful control in the context of friendship influence and early-onset use. J Abnorm Child Psychol. 2012; 40(7): 1045-1058.

One-Year Prediction of Pain Killer Use Among At-Risk Older Teens and Emerging Adults
The leading substance of misuse among teens after tobacco, alcohol, and marijuana is the use of pain killers. Very few longitudinal studies on prediction of pain killer use have been conducted among teens. This study examined the 1-year prediction of self-reported last 30-day pain killer use controlling for baseline 30-day painkiller use among 1186 alternative high school youth in California. Among demographic, behavioral, psychosocial, and environmental predictors, a multivariable model indicated that: (a) relatively higher levels of baseline pain killer use; (b) white ethnicity; (c) relatively lower levels of depressive symptoms (contrary to previous studies); and (d) those who live with both parents were more likely to report use of pain killer medications in the next year. It is speculated that those with relatively greater access to pain medication, within an at-risk social environment, are those who will use it later on. Sussman S, Rohrbach L, Spruijt-Metz D, Barnett E, Lisha N, Sun P. One-year prediction of pain killer use among at-risk older teens and emerging adults. J Drug Educ. 2012; 42(2): 195-210.

Attention Deficit/Hyperactivity Disorder Symptoms and Depression Symptoms as Mediators in the Intergenerational Transmission of Smoking Attention deficit/hyperactivity disorder and depression have been found to be comorbid with smoking behaviors, and all three behavioral syndromes have been shown to be familially transmitted. The present paper reports on the results of analyses testing whether child attention deficit/hyperactivity disorder and depression symptoms were mediators in the intergenerational transmission of cigarette smoking. Path analyses using bootstrapped mediation procedures were conducted on data from a community sample of 764 families (one or both parents and one adolescent offspring) from the Indiana University Smoking Survey. Parents reported on their smoking behaviors, ADHD, and depression and their child's ADHD, while offspring reported on their smoking behaviors and depression. Although fathers', and mothers' smoking status, depression, and ADHD were not significantly correlated with boys', smoking initiation, there was a significant mediated (indirect) pathway from mothers' depression to boys' smoking initiation through boys' depression. Several parental variables were significantly correlated with smoking initiation in girls, and the pathways from mothers' smoking status, mothers' ADHD, and fathers' smoking status to girls' smoking initiation were significantly mediated by girls' ADHD. For adolescent girls, the intergenerational transmission of ADHD appears to be important in understanding the intergenerational transmission of cigarette smoking. Sex differences in the intergenerational transmission of psychopathology as it leads to smoking initiation were also discussed. Zoloto A, Nagoshi C, Presson C, Chassin L. Attention Deficit/Hyperactivity Disorder symptoms and depression symptoms as mediators in the intergenerational transmission of smoking. Drug Alcohol Depend. 2012; 126(1-2): 147-155.

Demographic and Contextual Factors Associated with Inhalant Use Among Youth in Rural Alaska Abuse of harmful legal products that can be inhaled or ingested is a serious and growing problem in many rural Alaskan communities, and particularly so among preteens. This study analyzes data collected during baseline measurements of a 5-year NIH/NIDA-funded study entitled A Community Trial to Prevent Youth's Abuse of Harmful Legal Products in Alaska. Youth in 8 communities located throughout the state participated in a survey during the fall of 2009 to measure the prevalence and availability of harmful legal products (n=697). The goal of the analysis presented here is to compare the contextual factors of inhalant users and non-users in rural Alaskan communities. As reported in national surveys of substance use among youth, participants in this study indicated using alcohol more than any other substance. Inhalants were the second-most common substance abused, higher than either cigarettes or marijuana. Lifetime use varied among demographic factors such as age, gender and ethnicity as well as contextual factors including academic performance, parent employment, household living situation and income. When compared to non-users, significantly larger proportions of participants reporting lifetime inhalant use indicated easy availability of inhalants in their home, school and retail outlets. Users were also significantly more likely than non-users to have consumed alcohol. Results of this study may inform the development of effective interventions in other rural communities. Driscoll D, Dotterrer B, Collins D, Ogilvie K, Grube J, Johnson K. Demographic and contextual factors associated with inhalant use among youth in rural Alaska. Int J Circumpolar Health. 2012; 71: 1-4.

Concurrent and Predictive Relationships Between Compulsive Internet Use and Substance Use: Findings from Vocational High School Students in China and the USA Compulsive Internet Use (CIU) has increasingly become an area of research among process addictions. Largely based on data from cross-sectional studies, a positive association between CIU and substance use has previously been reported. This study presents gender and country-specific longitudinal findings on the relationships between CIU and substance use. Data were drawn from youth attending non-conventional high schools, recruited into two similarly implemented trials conducted in China and the USA. The Chinese sample included 1,761 students (49% male); the US sample included 1,182 students (57% male) with over half (65%) of the US youth being of Hispanic ethnicity. Path analyses were applied to detect the concurrent and predictive relationships between baseline and one-year follow-up measures of CIU level, 30-day cigarette smoking, and 30-day binge drinking. Results indicated that (1) CIU was not positively related with substance use at baseline. (2) There was a positive predictive relationship between baseline CIU and change in substance use among female, but not male students. (3) Relationships between concurrent changes in CIU and substance use were also found among female, but not male students. (4) Baseline substance use did not predict an increase in CIU from baseline to 1-year follow-up. While CIU was found to be related to substance use, the relationship was not consistently positive. More longitudinal studies with better measures for Internet Addiction are needed to ascertain the detailed relationship between Internet addiction and substance use. Sun P, Johnson C, Palmer P, Arpawong T, Unger J, Xie B, Rohrbach L, Spruijt-Metz D, Sussman S. Concurrent and predictive relationships between compulsive internet use and substance use: Findings from vocational high school students in China and the USA. Int J Environ Res Public Health. 2012; 9(3): 660-673.

Prior Substance Abuse and Related Treatment History Reported By Recent Victims Of Sexual Assault To inform intervention approaches, the current study examined prevalence and comorbidity of recent use and history of abuse of alcohol, marijuana, and other illicit drugs as well as history of substance treatment among a sample of female victims of sexual assault seeking post-assault medical care. Demographic variables and prior history of assault were also examined to

further identify factors relevant to treatment or prevention approaches. Participants were 255 women and adolescent girls seeking post sexual assault medical services who completed an initial follow-up assessment on average within 3months post-assault. The majority (72.9%) reported recent substance use prior to assault, approximately 40% reported prior substance abuse history, and 12.2% reported prior substance treatment history. Prior history of assault was associated with recent drug use and history of drug abuse as well as substance treatment. Among those with prior histories of substance abuse and assault, assault preceded substance abuse onset in the majority of cases. Almost all of those with prior treatment history reported recent drug or alcohol use. A portion of sexual assault survivors seen for acute medical services may benefit from facilitated referral for substance abuse treatment in addition to counseling at the time of screening. Assessment and intervention approaches should target alcohol, marijuana, and other illicit drug use and abuse. Substance use and associated impairment may serve as a rape tactic by perpetrators of assault. Substance use at the time of assault does not imply blame on the part of assault victims. Previous findings indicate that rape poses high risk of PTSD particularly among women with prior history of assault. Screening and intervention related to substance abuse should be done with recognition of the increased vulnerability it may pose with regard to assault and the high risk of PTSD within this population. Resnick H, Walsh K, Schumacher J, Kilpatrick D, Acierno R. Prior substance abuse and related treatment history reported by recent victims of sexual assault. Addict Behav. 2012; 38(4): 2074-2079.

Group Influences On Individuals' Drinking and Other Drug Use At Clubs This article examines effects of the social group on individual alcohol and drug use upon entry and exit from the club. Based on collected biological measurements of alcohol and other drug use, this study explores whether social group indicators (e.g., group characteristics) are predictive of alcohol and other drug use for individual club patrons. A total of 368 social groups, representing 986 individuals (50.7% female), were anonymously surveyed, and biological measures of alcohol and other drug use were collected at entrance and exit to clubs on a single evening. Both individual and group-level indicators were assessed. Because data were clustered by club, event, and group, mixed-model regressions were conducted to account for non-independence. Group indicators of high blood alcohol concentration were being in a group that intends to get drunk, that has at least one member who regularly gets drunk, and that has discrepancies in its expectations regarding drug use. Group indicators related to cocaine use were high levels of drug use expected among group members, little discrepancy among the group members regarding the drug use expected, and high levels of intentions to get drunk. In addition, older groups were more likely to have higher levels of cocaine use. There were less consistent findings regarding group effects on marijuana use. The most consistent finding was that high drug use expectations were related to higher levels of marijuana use. Together, these data suggest that strategies should focus on recognizing group indicators as risks for group members. Promoting social responsibility for group members may create safer club experiences among young adults. These efforts could model designated-driver programs as a way to increase safety and social responsibility. (J. Stud. Alcohol Drugs, 74, 280-287, 2013). Miller B, Byrnes H, Branner A, Johnson M, Voas R. Group influences on individuals' drinking and other drug use at clubs. J Stud Alcohol Drugs. 2013; 74(2): 280-287.

The Effects Of Employment Among Adolescents At-Risk For Future Substance Use This paper explores the association between work intensity, alcohol and/or other drug (AOD) use, and related risk factors and consequences among an at-risk youth sample that has received a first-time AOD offense. This study extends previous research focused primarily on school-based samples. The authors examined the association between work intensity, AOD use, AOD-related consequences,

and social environment among adolescents referred to a diversion program called Teen Court (N=193). Participants were surveyed prior to the start of the Teen Court program. Mean age was 17 (SD=1.1), 67% of the sample was male; 45% Hispanic or Latino/a; 45.1% White; 10% Other. Greater work intensity among these youth was related to greater alcohol-related negative consequences and greater contact with co-workers who engaged in risky behaviors, but it was not significantly associated with past month AOD use. Understanding the relationship between work intensity and AOD use among youth who are at-risk is critical to informing clinicians and public officials about the potential effects of employment in this population. Findings suggest that work intensity may be associated with negative consequences from alcohol use and increased contact with risky co-workers, all of which could contribute to the development of problems in the future. Osilla K, Hunter S, Ewing B, Ramchand R, Miles J, D'Amico E. The effects of employment among adolescents at-risk for future substance use. Addict Behav. 2013; 38(3): 1616-1619.

Driving Decisions When Leaving Electronic Music Dance Events: Driver, Passenger, and Group Effects The goal of this article was to identify characteristics of drivers and passengers that predicted peer groups whose drivers exit dance clubs with alcohol levels indicative of impairment (blood alcohol content [BAC] e 0.05 g/dL). The authors used the portal survey methodology to randomly sample groups of electronic music dance event (EMDE) patrons as they entered and exited a club. From May through November 2010, data were collected from 38 EMDEs hosted by 8 clubs in the San Francisco Bay area. Data included in these analyses are results from breath samples for measuring BAC and self-report data on demographics, recent drinking history drinking, drinking intentions, travel to and from the clubs, and the familiarity/experience with other group members. These data were collected from a subset of 175 drivers and 272 passengers. Although drivers drank less than passengers, one driver in 5 groups had a BAC indicative of elevated crash risk (BAC e 0.05 g/dL). Groups of drivers and/or passengers with a recent history of binge drinking were more likely to have drivers with BACs e 0.05 g/dL. One unanticipated finding was that drivers who knew more group members relatively well were more likely to exit the club with a BAC e 0.05 g/dL. Additionally, the authors found that groups with all female passengers were at greater risk for having a driver whose BAC was e 0.05 g/dL. Some group characteristics predicted drivers who exit clubs with BACs e 0.05 g/dL. One intervention strategy to promote safety might be to encourage group members to reconsider who is sober enough to drive away from the club; for some groups, a change of drivers would be a safer choice, because a passenger may have a relatively safe BAC. Groups of females appear to have a particularly elevated risk of having a driver who's BAC exceeds 0.05 g/dL, and new intervention efforts should be particularly directed to these at-risk groups. Johnson M, Voas R, Miller B. Driving decisions when leaving electronic music dance events: Driver, passenger, and group effects. Traffic Inj Prev. 2012; 13(6): 577-584.

The Association Between Parent Early Adult Drug Use Disorder and Later Observed Parenting Practices and Child Behavior Problems: Testing Alternate Models This study tested the association between parent illicit drug use disorder (DUD) in early adulthood and observed parenting practices at ages 27-28 and examined the following 3 theoretically derived models explaining this link: (a) a disrupted parent adult functioning model,(b) a preexisting parent personality factor model, and (c) a disrupted adolescent family process model. Associations between study variables and child externalizing problems also were examined. Longitudinal data linking 2 generations were drawn from the Seattle Social Development Project (SSDP) and The SSDP Intergenerational Project (TIP), and included 167 parents and their 2- to 8-year-old child. Path modeling revealed that parent DUD in early adulthood predicted later observed low-skilled parenting, which was related to child externalizing problems. The preexisting parent personality

factor model was supported. Parent negative emotionality accounted for the association between parents early adult DUD and later parenting practices. Parent negative emotionality also was related directly to child externalizing behavior. Limited support for the disrupted transition to adulthood model was found. The disrupted adolescent family process model was not supported. Results suggest that problem drug use that occurs early in adulthood may affect later parenting skills, independent of subsequent parent drug use. Findings highlight the importance of parent negative emotionality in influencing his or her own problem behavior, interactions with his or her child, and his or her child's problem behavior. Prevention and treatment programs targeting young adult substance use, poor parenting practices, and child behavior problems should address parent personality factors that may contribute to these behaviors. Bailey J, Hill K, Guttmannova K, Oesterle S, Hawkins J, Catalano R, McMahon R. The association between parent early adult drug use disorder and later observed parenting practices and child behavior problems: Testing alternate models. Dev Psychol. 2012; doi: 10.1037/a0029235: 1-13.

Individual Differences And Social Influences On The Neurobehavioral Pharmacology Of Abused Drugs The interaction of drugs with biologic targets is a critical area of research, particularly for the development of medications to treat substance use disorders. In addition to understanding these drug-target interactions, however, there is a need to understand more fully the psychosocial influences that moderate these interactions. The first section of this review introduces some examples from human behavioral pharmacology that illustrate the clinical importance of this research. The second section covers preclinical evidence to characterize some of the key individual differences that alter drug sensitivity and abuse vulnerability, related primarily to differences in response to novelty and impulsivity. Evidence is presented to indicate that critical neuropharmacological mechanisms associated with these individual differences involve integrated neurocircuits underlying stress, reward, and behavioral inhibitory processes. The third section covers social influences on drug abuse vulnerability, including effects experienced during infancy, adolescence, and young adulthood, such as maternal separation, housing conditions, and social interactions (defeat, play, and social rank). Some of the same neurocircuits involved in individual differences also are altered by social influences, although the precise neurochemical and cellular mechanisms involved remain to be elucidated fully. Finally, some speculation is offered about the implications of this research for the prevention and treatment of substance abuse. Bardo M, Neisewander J, Kelly T. Individual differences and social influences on the neurobehavioral pharmacology of abused drugs. Pharmacol Rev. 2013; 65(1): 255-290.

Does Parentification Place Mexican-heritage Youth at Risk for Substance Use? Identifying the Intervening Nature of Parent-child Communication about Alcohol Past research on parentification suggests that adopting adult responsibilities to the point at which the child plays a parental role places children at risk for poor mental and behavioral health outcomes. Since family relations are particularly important in Mexican culture, two hypotheses were posed to examine the indirect effects of parentification on Mexican-heritage youths substance use via parent-child communication about alcohol, while examining the moderating effects of parent-child closeness. Mexican-heritage youth (N = 697) from 23 public middle schools in Phoenix, AZ completed surveys at three waves. Structural equation modeling results provided partial support for the hypotheses. Mexican-heritage youth experiencing problem-solving parentification were more likely to talk with a parent about alcohol and, in turn, less likely to use substances. This mediation effect, however, was not found with respect to adult parentification, and parent-child closeness was not a significant moderator. Implications for the beneficial effects of problem-solving parentification are discussed. Shin Y, Hecht M. Does Parentification place Mexican-heritage youth at risk for

substance use? Identifying the intervening nature of parent-child communication about alcohol. J Adolesc. 2013; 36(1): 149-159.

Racial and Ethnic Differences in Diurnal Cortisol Rhythms in Preadolescents: The Role of Parental Psychosocial Risk and Monitoring Racial/ethnic minorities experience persistent health disparities due in part to their exposure to chronic SES and psychosocial risk. The hypothalamic-pituitary-adrenal axis and its hormonal end product, cortisol, are believed to mediate the associations between chronic stress and poor health. In this study, racial/ethnic differences in diurnal salivary cortisol rhythms in 179 preadolescent youths and the contributing roles of SES risk, psychosocial risk, perceived discrimination, harsh parenting, and parental monitoring were examined. The analyses revealed racial/ethnic differences in diurnal cortisol rhythms, with African Americans having significantly flatter morning-to-evening cortisol slopes than Caucasians and with Latinos having significantly lower evening cortisol levels than Caucasians. Greater psychosocial risk and less parental monitoring were associated with flatter cortisol slopes. Racial/ethnic differences on the cortisol measures persisted when controlling for SES, psychosocial risk, and parenting quality. The need to assess chronic risk across the lifespan and disentangle possible genetic from environmental contributors is discussed. Martin C, Bruce J, Fisher P. Racial and ethnic differences in diurnal cortisol rhythms in preadolescents: The role of parental psychosocial risk and monitoring. Horm Behav. 2012; 61(5): 661-668.

The Association Between Implicit And Explicit Attitudes Toward Smoking And Support For Tobacco Control Measures This study examined the association between implicit and explicit attitudes toward smoking and support for tobacco control policies. Participants were from an ongoing longitudinal study of the natural history of smoking who also completed a web-based assessment of implicit attitudes toward smoking (N = 1,337). Multiple regressions was used to test the association between covariates (sex, age, educational attainment, parent status, and smoking status), implicit attitude toward smoking, and explicit attitude toward smoking and support for tobacco control policies. The moderating effect of the covariates on the relation between attitudes and support for policies was also tested. Females, those with higher educational attainment, parents, and nonsmokers expressed more support for tobacco control policy measures. For nonsmokers, only explicit attitude was significantly associated with support for policies. For smokers, both explicit and implicit attitudes were significantly associated with support. The effect of explicit attitude was stronger for those with lower educational attainment. Both explicit and implicit smoking attitudes are important for building support for tobacco control policies, particularly among smokers. More research is needed on how to influence explicit and implicit attitudes to inform policy advocacy campaigns. Macy J, Chassin L, Presson C. The association between implicit and explicit attitudes toward smoking and support for tobacco control measures. Nicotine Tob Res. 2013; 15(1): 291-296.

The Development of Conventional Sexual Partner Trajectories Among African American Male Adolescents African American male youth disproportionately report involvement with multiple sexual partners, which increases their risk for sexually transmitted infections and initiation of unplanned pregnancies. Little is known about the developmental precursors of sexual partner trajectories among African American male youth. Moreover, few studies focus on the many African American youth who evince highly conventional sexual partner trajectories, i.e., youth who have only one partner or abstain from sexual activity across time. Using four waves of data from a longitudinal study, the authors hypothesized that an accumulation of social and economic disadvantages in early adolescence would negatively influence youths' conventional sexual partner trajectories in late adolescence. They expected these disadvantages to affect youths' receipt of

protective family processes and their reports of a set of intrapersonal processes (self-regulation, hope, and low levels of anger) linked to generally conventional behavior. Hypotheses were tested with data from 315 African American male youth from 11 to 18.5 years of age and their primary caregivers. These results supported the hypotheses. Socioeconomic disadvantages during preadolescence predicted less involvement in conventional sexual partner trajectories from ages 16 to 18.5 years. This association was mediated by protective family processes and a set of interrelated intrapersonal protective processes. Preventive interventions designed to promote protective parenting and intrapersonal processes can be expected to promote sexual behavior trajectories characterized by abstinence or relations with very few partners. Kogan S, Yu T, Brody G, Allen K. The development of conventional sexual partner trajectories among African American male adolescents. Arch Sex Behav. 2012; doi: 10.1007/s10508-012-0025-5: 1-10.

From Antisocial Behavior to Violence: A Model for the Amplifying Role of Coercive Joining in Adolescent Friendships Aggression is one of the more stable characteristics of child and adolescent development, and violent behavior in early adulthood is often foreshadowed by aggressive behavior in childhood and early adolescence. Considerable evidence has linked coercive family interactions to aggressive behavior in childhood, but less research has been conducted on the joint role of family and peer interaction in the escalation of aggression to violence in adulthood. The authors coded family interactions at age 12-13 and friendship interaction at age 16-17 in a multiethnic sample of youth and families. Violence in young adulthood (age 22-23) was measured using self-report, criminal records, and parent report. They tested the hypothesis that a process of 'coercive joining' in friendship interactions mediated the relationship between coercive family interactions and serious violence. The authors found that observed coercive joining in friendships at age 16-17 predicted early-adulthood violent behavior over and above an established tendency toward antisocial behavior. They also found that observed coercive family interactions at age 12 predicted early-adulthood violence, and that coercive joining with friends fully mediated this link. These results significantly extend coercion theory by suggesting that coercive joining in the context of peer groups is an additional mechanism by which coercive processes in the family are extended and amplified to violent behavior in early adulthood. These findings suggest the importance of addressing both individual interpersonal skills and self-organizing peer groups when intervening to prevent violent behavior. Van Ryzin M, Dishion T. From Antisocial Behavior To Violence: A Model For The Amplifying Role Of Coercive Joining In Adolescent Friendships. J Child Psychol Psychiatry. 2012; DOI: 10.1111/jcpp.12017 : 1-9.

Negative Emotionality and Externalizing Problems In Toddlerhood: Overreactive Parenting as A Moderator of Genetic Influences The current study examines the interplay between parental overreactivity and children's genetic backgrounds as inferred from birth parent characteristics on the development of negative emotionality during infancy, and in turn, to individual differences in externalizing problems in toddlerhood. The sample included 361 families linked through adoption (birth parents and adoptive families). Data were collected when the children were 9, 18, and 27 months old. Results indicated links between individual levels and changes in negative emotionality during infancy and toddlerhood to externalizing problems early in the third year of life. Findings also revealed an interaction between birth mother negative affect and adoptive mother overreactive parenting on children's negative emotionality. This Genotype × Environment interaction predicted externalizing problems indirectly through its association with negative emotionality and revealed stronger effects of genetic risk for children with less overreactive parenting from their mothers. Limitations of this study and directions for future research are discussed. Lipscomb S, Leve L, Shaw D, Neiderhiser J, Scaramella L, Ge X, Conger R, Reid J, Reiss D. Negative emotionality and

externalizing problems in toddlerhood: overreactive parenting as a moderator of genetic influences. Dev Psychopathol. 2012; 24(1): 167-179.

Psychological Symptoms Linking Exposure to Community Violence and Academic Functioning in African American Adolescents African American adolescents are exposed disproportionately to community violence, increasing their risk for emotional and behavioral symptoms that can detract from learning and undermine academic outcomes. The present study examined whether aggressive behavior and depressive and anxious symptoms mediated the association between exposure to community violence and academic functioning, and if the indirect effects of community violence on academic functioning differed for boys and girls, in a community sample of urban African American adolescents (N = 491; 46.6% female). Structural equation modeling was used to examine the indirect effect of exposure to community violence in grade 6 on grade 8 academic functioning. Results revealed that aggression in grade 7 mediated the association between grade 6 exposures to community violence and grade 8 academic functioning. There were no indirect effects through depressive and anxious symptoms, and gender did not moderate the indirect effect. Findings highlight the importance of targeting aggressive behavior for youth exposed to community violence to not only improve their behavioral adjustment but also their academic functioning. Implications for future research are discussed. Busby D, Lambert S, Ialongo N. Psychological symptoms linking exposure to community violence and academic functioning in African American adolescents. J Youth Adolesc. 2013; 42(2): 250-262.

Marital Hostility and Child Sleep Problems: Direct and Indirect Associations Via Hostile Parenting The current study examined two family process predictors of parent-reported child sleep problems at 4.5 years in an adoption sample: marital hostility and hostile parenting. Participants were 361 linked triads of birth parents, adoptive parents, and adopted children. The authors examined direct and indirect pathways from marital hostility to child sleep problems via hostile parenting. Mothers' marital hostility at 9 months was associated with child sleep problems at 4.5 years. Fathers' marital hostility at 9 months evidenced an indirect effect on child sleep problems at 4.5 years via fathers' hostile parenting at 27 months. Findings were significant even after controlling for genetic influences on child sleep (i.e., birth parent internalizing disorders). The findings suggest targets for prevention and intervention programs that are potentially modifiable (e.g., hostile parenting, marital hostility), and inform theory by demonstrating that relations among marital hostility, hostile parenting, and child sleep problems are significant after accounting for genetic influences. Rhoades K, Leve L, Harold G, Mannering A, Neiderhiser J, Shaw D, Natsuaki M, Reiss D. Marital hostility and child sleep problems: Direct and indirect associations via hostile parenting. J Fam Psychol. 2012; 26(4): 488-498.

Economic Analysis of a Multi-Site Prevention Program: Assessment of Program Costs and Characterizing Site-level Variability Programmatic cost analyses of preventive interventions commonly have a number of methodological difficulties. To determine the mean total costs and properly characterize variability, one often has to deal with small sample sizes, skewed distributions, and especially missing data. Standard approaches for dealing with missing data such as multiple imputation may suffer from a small sample size, a lack of appropriate covariates, or too few details around the method used to handle the missing data. In this study, the authors estimate total programmatic costs for a prevention trial evaluating the Strong African American Families-Teen program. This intervention focuses on the prevention of substance abuse and risky sexual behavior. To account for missing data in the assessment of programmatic costs the authors compare multiple imputations to probabilistic sensitivity analysis. The latter approach uses collected cost

data to create a distribution around each input parameter. They found that with the multiple imputation approach, the mean (95% confidence interval) incremental difference was $2,149 ($397, $3,901). With the probabilistic sensitivity analysis approach, the incremental difference was $2,583 ($778, $4,346). Although the true cost of the program is unknown, probabilistic sensitivity analysis may be a more viable alternative for capturing variability in estimates of programmatic costs when dealing with missing data, particularly with small sample sizes and the lack of strong predictor variables. Further, the larger standard errors produced by the probabilistic sensitivity analysis method may signal its ability to capture more of the variability in the data, thus better informing policymakers on the potentially true cost of the intervention. Corso P, Ingels J, Kogan S, Foster E, Chen Y, Brody G. Economic analysis of a multi-site prevention program: assessment of program costs and characterizing site-level variability. Prev Sci. 2013; DOI: 10.1007/s11121-012-0316-z : 1-10.

Predictive Validity Of Established Cut Points For Risk and Protective Factor Scales From The Communities That Care Youth Survey Community coalitions are a popular strategy to coordinate activities and resources to prevent adolescent substance use and delinquent behavior. Despite early evidence of their lack of effectiveness, a new generation of community coalitions has shown positive results in preventing youth substance use and delinquency. This success can be attributed to coalition decision making focused on reducing local risk factors and increasing local protective factors through the use of evidence-based prevention programs. A previous study using cross-sectional data established cut point values for scales measuring risk and protective factors on the Communities That Care Youth Survey (CTCYS) to identify high levels of risk and low levels of protection in communities on each scale. The current study extended this previous research by using longitudinal data to assess the validity of risk and protective factor cut point values in predicting substance use and delinquent behavior 1 year after risk and protection were measured. The findings demonstrate the predictive validity of cut points for risk and protective factor scales measured by the CTCYS and suggest their utility in guiding prevention efforts. Briney J, Brown E, Hawkins J, Arthur M. Predictive validity of established cut points for risk and protective factor scales from the Communities That Care Youth Survey. J Prim Prev. 2012; 33(5-6): 249-258.

Evaluation of the Psychometric Properties of the Revised Inventory of the Dimensions of Emerging Adulthood (IDEA-R) in a Sample of Continuation High School Students It is now presumed that youth do not move directly from adolescence to adulthood, but rather pass through a transitional period, “emerging adulthood.” The Revised Inventory of the Dimensions of Emerging Adulthood (IDEA-R) is a self-report instrument developed to examine the attributes of this period. “At-risk” youth appear to enter emerging adulthood developmental tasks at a slightly earlier age than general population youth. In the present study, a 21-item version of the IDEA was administered to a sample of 1676 “at-risk” continuation (alternative) high school students in Southern California. Principal component factor analysis with orthogonal rotation revealed three factors the authors labeled "Identity Exploration," “Experimentation/Possibilities,” and “Independence.” Overall, the measure demonstrated high internal consistency. Construct validity analyses indicated that the measure was correlated with demographics, risk behaviors, and psychological measures. The authors conclude that the IDEA-R is a useful instrument for measuring emerging adulthood in at-risk populations. Lisha N, Grana R, Sun P, Rohrbach L, Spruijt-Metz D, Reifman A, Sussman S. Evaluation of the psychometric properties of the Revised Inventory of the Dimensions of Emerging Adulthood (IDEA-R) in a sample of continuation high school students. Eval Health Prof. 2012; doi:10.1177/0163278712452664 1-23.

The Application of Meta-Analysis within A Matched-Pair Randomized Control Trial: An Illustration Testing The Effects of Communities That Care on Delinquent Behavior Use of meta-analytic strategies to test intervention effects is an important complement to traditional design-based analyses of intervention effects in randomized control trials. In the present paper, the authors suggest that meta-analyses within the context of matched-pair designs can provide useful insight into intervention effects. They illustrate the advantages to this analytic strategy by examining the effectiveness of the Communities That Care (CTC) prevention system on 8th-grade delinquent behavior in a randomized matched-pair trial. They estimate the intervention effect within each of the matched-pair communities, aggregate the effect sizes across matched pairs to derive an overall intervention effect, and test for heterogeneity in the effect of CTC on delinquency across matched pairs of communities. The meta-analysis finds that CTC reduces delinquent behavior and that the effect of CTC on delinquent behavior varies significantly across communities. The use of meta-analysis in randomized matched-pair studies can provide a useful accompaniment to other analytic approaches because it opens the possibility of identifying factors associated with differential effects across units or matched pairs in the context of a randomized control trial. Monahan K, Hawkins J, Abbott R. The application of meta-analysis within a matched-pair randomized control trial: An illustration testing the effects of Communities That Care on delinquent behavior. Prev Sci. 2013; 14(1): 1-12.

Assessing Motivational Interviewing Integrity For Group Interventions With Adolescents The group format is commonly used in alcohol and other drug (AOD) adolescent treatment settings, but little research exists on the use of motivational interviewing (MI) in groups. Further, little work has assessed the integrity of MI delivered in group settings. This study describes an approach to evaluate MI integrity using data from a group MI intervention for at-risk youth. Using the Motivational Interviewing Treatment Integrity (MITI) scale, version 3.1, the authors coded 140 group sessions led by 3 different facilitators. Four trained coders assessed the group sessions. Agreement between raters was evaluated using a method based on limits of agreement, and key decisions used to monitor and calculate group MI integrity are discussed. Results indicated that there was adequate agreement between raters; the authors also found differences on use of MI between the MI-intervention group and a usual-care group on MI global ratings and behavioral counts. This study demonstrates that it is possible to determine whether group MI is implemented with integrity in the group setting and that MI in this setting is different from what takes place in usual care. D'Amico E, Osilla K, Miles J, Ewing B, Sullivan K, Katz K, Hunter S. Assessing Motivational interviewing integrity for group interventions with adolescents. Psychol Addict Behav. 2012; 26(4): 994-1000.

Applying Ecodevelopmental Theory and the Theory of Reasoned Action to Understand HIV Risk Behaviors Among Hispanic Adolescents HIV/AIDS is listed as one of the top 10 reasons for the death of Hispanics between the ages of 15 and 54 in the United States. This cross sectional, descriptive secondary study proposed that using both the systemic (ecodevelopmental) and the individually focused (theory of reasoned action) theories together would lead to an increased understanding of the risk and protective factors that influence HIV risk behaviors in this population. The sample consisted of 493 Hispanic adolescent 7th and 8th graders and their immigrant parents living in Miami, Florida. Structural Equation Modeling (SEM) was used for the data analysis. Family functioning emerged as the heart of the model, embedded within a web of direct and mediated relationships. The data support the idea that family can play a central role in the prevention of Hispanic adolescents ' risk behaviors. Ortega J, Huang S, Prado G. Applying

ecodevelopmental theory and the theory of reasoned action to understand HIV risk behaviors among Hispanic adolescents. Hisp Health Care Int. 2012; 10(1): 42-52.

Developing Empirically Based, Culturally Grounded Drug Prevention Interventions for Indigenous Youth Populations This article describes the relevance of a culturally grounded approach toward drug prevention development for indigenous youth populations. This approach builds drug prevention from the "ground up" (i.e., from the values, beliefs, and worldviews of the youth that are the intended consumers of the program) and is contrasted with efforts that focus on adapting existing drug prevention interventions to fit the norms of different youth ethnocultural groups. The development of an empirically based drug prevention program focused on rural Native Hawaiian youth is described as a case example of culturally grounded drug prevention development for indigenous youth; the impact of this effort on the validity of the intervention and on community engagement and investment in the development of the program are discussed. Finally, implications of this approach for behavioral health services and the development of an indigenous prevention science are discussed. Okamoto S, Helm S, Pel S, McClain L, Hill A, Hayashida J. Developing empirically based, culturally grounded drug prevention interventions for indigenous youth populations. J Behav Health Serv Res. 2012; published online November 28, 2012: 1-12.

The Development of Videos in Culturally Grounded Drug Prevention for Rural Native Hawaiian Youth The purpose of this study was to adapt and validate narrative scripts to be used for the video components of a culturally grounded drug prevention program for rural Native Hawaiian youth. Scripts to be used to film short video vignettes of drug-related problem situations were developed based on a foundation of pre-prevention research funded by the National Institute on Drug Abuse. Seventy-four middle- and high-school-aged youth in 15 focus groups adapted and validated the details of the scripts to make them more realistic. Specifically, youth participants affirmed the situations described in the scripts and suggested changes to details of the scripts to make them more culturally specific. Suggested changes to the scripts also reflected preferred drug resistance strategies described in prior research, and varied based on the type of drug offerer described in each script (i.e., peer/friend, parent, or cousin/sibling). Implications for culturally grounded drug prevention are discussed. Okamoto S, Helm S, McClain L, Dinson A. The Development of videos in culturally grounded drug prevention for rural Native Hawaiian youth. J Prim Prev. 2012; 33(5-6): 259-269.

Conditioned Place Preference and Aversion For Music In A Virtual Reality Environment The use of a virtual reality environment (VRE) enables behavioral scientists to create different spatial contexts in which human participants behave freely, while still confined to the laboratory. In this article, VRE was used to study conditioned place preference (CPP) and aversion (CPA). In Experiment 1, half of the participants were asked to visit a house for 2 min with consonant music and then they were asked to visit an alternate house with static noise for 2 min, whereas the remaining participants did the visits in reverse order. In Experiment 2, the authors used the same design as Experiment 1, except for replacing consonant music with dissonant music. After conditioning in both experiments, the participants were given a choice between spending time in the two houses. In Experiment 1, participants spent more time in the house associated with the consonant music, thus showing a CPP toward that house. In Experiment 2, participants spent less time in the house associated with the dissonant music, thus showing a CPA for that house. These results support VRE as a tool to extend research on CPP/CPA in humans. Molet M, Billiet G, Bardo M. Conditioned place preference and aversion for music in a virtual reality environment. Behav Processes. 2013; 92: 31-35.

BEHAVIORAL AND INTEGRATIVE TREATMENT RESEARCH

Alcohol Use and HIV Risk among Juvenile Drug Court Offenders Juvenile drug courts (JDC) largely focus on marijuana and other drug use interventions. Yet, JDC offenders engage in other high-risk behaviors, such as alcohol use and sexual risk behaviors, which can compromise their health, safety and drug court success. An examination of alcohol use and sexual risk behaviors among 52 male substance abusing young offenders found that over 50% were using alcohol, 37% reported current marijuana use and one-third of all sexual intercourse episodes were unprotected. After accounting for recent marijuana use, the odds of a juvenile having vaginal or anal sex was 6 times greater if they had recently used alcohol. Juvenile drug courts may benefit from delivering alcohol and sexual risk reduction interventions to fully address the needs of these young offenders. Tolou-Shams M, Houck CD, Nugent N, Conrad SM, Reyes A, Brown LK. Alcohol use and HIV risk among juvenile drug court offenders. J Soc Work Pract Addict. 2012; 12(2): 178-188.

Emotionally Avoidant Language in the Parenting Interviews of Substance-Dependent Mothers Parenting and emotion regulation are two known, and potentially interrelated, areas of impairment among substance-abusing mothers. In this study, the authors examine substance-abusing mothers' (positive and negative) emotion language word use during their discussion of negative parenting experiences on the Parent Development Interview for its association with reflective functioning (RF), recent substance-use history, and sensitivity to child cues. Within a sample of 47 methadone-maintained mothers, the authors evaluate the hypothesis that linguistic evidence of emotional avoidance (more frequent positive feeling words and less frequent negative emotion words) will be associated with lower RF, more recent substance use, and more insensitive parenting. Further, they evaluate whether language use mediates the association between self-focused RF and insensitive parenting. Results of hierarchical regressions suggest that more frequent positive feeling word use, but not negative emotion word use, is associated with lower RF, more recent substance use, and lower sensitivity to child cues. Positive feeling word use partially mediates the association between self-focused RF and insensitive parenting. Results are discussed in the context of their contribution to the literature on emotion and parenting in substance-abusing populations. Borelli JL, West JL, Decoste C, Suchman NE. Emotionally avoidant language in the parenting interviews of substance-dependent mothers: associations with reflective functioning, recent substance use, and parenting behavior. Infant Ment Health J. 2012; 33(5): 506-519.

Attachment-Based Intervention for Substance-Using Mothers: A Preliminary Test of the Proposed Mechanisms Of Change Although randomized controlled trials examining the efficacy of attachment-based interventions have been increasing in recent years, adequate measurement of treatment integrity, integrity-outcome associations, and mechanisms of change has been rare. The aim of this investigation was to conduct a rigorous test of proposed mechanisms of change in the Mothers and Toddlers Program (MTP) treatment model, a 12-session, attachment-based individual therapy for substance-using mothers of children birth to 3 years of age. The MTP aims to improve maternal reflective functioning (RF) and representation quality (RQ) to bring about second-order change in maternal caregiving behavior. Following guidelines from M.K. Nock (2007), it was hypothesized that (a) therapist adherence to unique MTP treatment components would uniquely predict improvement in RF and RQ and that (b) improvement in RF and RQ would function as unique mechanisms of change (when compared with other potential mechanisms-reduction in depression and increase in abstinence from drug use) in the improvement of caregiving behavior. Findings supported each hypothesis, confirming the proposed mechanisms of the treatment model. However, improvement in maternal depression also uniquely predicted improvement in caregiving

behavior. Results underscore the potential value of attachment-based parenting interventions for improving mother-child relations and the importance of providing these interventions in clinic settings where mothers have access to comprehensive care (e.g., psychiatric services). Suchman NE, Decoste C, Rosenberger P, McMahon TJ. Attachment-based intervention for substance-using mothers: a preliminary test of the proposed mechanisms of change. Infant Ment Health J. 2012 Jul 1; 33(4): 360-371.

Predictors of Treatment Response in Adolescents with Comorbid Substance Use Disorder and Attention-Deficit/Hyperactivity Disorder Attention-Deficit/ Hyperactivity Disorder (ADHD) frequently co-occurs with substance use disorder (SUD) and is associated with poor substance-use treatment outcomes. A trial evaluating osmotic-release oral system methylphenidate (OROS-MPH) for adolescents with ADHD and SUD, concurrently receiving behavioral therapy, revealed inconsistent medication effects on ADHD or SUD. Clinical care for this population would be advanced by knowledge of treatment outcome predictors. Data from the randomized placebo-controlled trial (n = 299) were analyzed. Significant treatment predictors included: 1) Substance use severity, associated with poorer ADHD and SUD outcomes, 2) ADHD severity, associated with better ADHD and SUD outcomes, 3) comorbid conduct disorder, associated with poorer ADHD outcomes, and 4) court-mandated status, associated with better SUD outcomes but poorer treatment completion. An interaction effect showed that OROS-MPH improved SUD outcomes in adolescents with comorbid conduct disorder compared to placebo. While severe SUD may require more intensive psychosocial treatment, OROS-MPH may improve substance treatment outcomes in adolescents with co-morbid attention and conduct problems. Tamm L, Trello-Rishel K, Riggs P, Nakonezny PA, Acosta M, Bailey G, Winhusen T. Predictors of treatment response in adolescents with comorbid substance use disorder and attention-deficit/hyperactivity disorder. J Subst Abuse Treat. 2013 Feb; 44(2): 224-230.

Integration of Parenting Skills Education and Interventions in Addiction Treatment Children of parents with substance use disorders are at risk for various adverse outcomes, and maladaptive parenting behaviors seem to be an important mediator of this risk. Although numerous research studies have highlighted the promise of parenting interventions in modifying parenting behavior, very little is known about the integration of parenting skills education and interventions into addiction treatment programs. In this study, a convenience sample of 125 addiction treatment programs in the United States was drawn. A key staff member was interviewed to gather basic information about the extent and nature of parenting skills education and interventions offered at their program. In addition, respondents were asked to rate the importance of parenting skills relative to other addiction treatment priorities. Descriptive analyses revealed that 43% reported some form of parenting classes, but few used a structured curriculum. Given the known beneficial influence of effective parenting practices on reducing adverse childhood outcomes, it is surprising that relatively few substance abuse treatment programs have adopted structured parenting skills interventions as part of their standard service offerings. More research is warranted on the extent to which parenting skills interventions are integrated into the continuum of services available to parents with a substance use disorder. Arria AM, Mericle AA, Rallo D, Moe J, White WL, Winters KC, O'Connor G. Integration of parenting skills education and interventions in addiction treatment. J Addict Med. 2013 Jan-Feb; 7(1): 1-7.

Evolution of Concept, but Not Action, in Addiction Treatment The Western approach to addiction treatment involves a medical or disease orientation to understanding the onset, course, and management of addiction, and a clinical goal of abstinence or very significant reductions in drug use, usually with a combination of behavioral and pharmacological interventions. Even within this Western approach, and despite several consensually accepted features of addiction, a significant mismatch remains between what this culture has come to accept as the nature of the disease and how that same culture continues to treat the disease. This paper discusses the evolution of these Western concepts over the past decade without a corresponding evolution in the nature, duration, or evaluation standards for addiction treatment. (1) Here, the authors take the position that continuing care and adaptive treatment protocols, combining behavioral therapies, family and social supports, and, where needed, medications show much promise to address the typically chronic, relapsing, and heterogeneous nature of most cases of serious addiction. By extension, methods to evaluate effectiveness of addiction treatment should focus upon the functional status of patients during the course of their treatment instead of post-treatment, as is the evaluation practice used with most other chronic illnesses. Arria AM, McLellan AT. Evolution of concept, but not action, in addiction treatment. Subst Use Misuse. 2012 Jun-Jul; 47(8-9): 1041-1048.

Is Exposure to an Effective Contingency Management Intervention Associated with More Positive Provider Beliefs? This study empirically examined opinions of treatment providers regarding contingency management (CM) programs while controlling for experience with a specific efficacious CM program. In addition to empirically describing provider opinions, the authors examined whether the opinions of providers at the sites that implemented the CM program were more positive than those of matched providers at sites that did not implement it. Participants from 7 CM treatment sites (n = 76) and 7 matched nonparticipating sites (n = 69) within the same nodes of the National Institute of Drug Abuse Clinical Trials Network completed the Provider Survey of Incentives (PSI), which assesses positive and negative beliefs about incentive programs. An intent-to-treat analysis found no differences in the PSI summary scores of providers in CM program versus matched sites, but correcting for experience with tangible incentives showed significant differences, with providers from CM sites reporting more positive opinions than those from matched sites. Some differences were found in opinions regarding costs of incentives, and these generally indicated that participants from CM sites were more likely to see the costs as worthwhile. The results from the study suggest that exposing community treatment providers to incentive programs may itself be an effective strategy in prompting the dissemination of CM interventions. Kirby KC, Carpenedo CM, Stitzer ML, Dugosh KL, Petry NM, Roll JM, Saladin ME, Cohen AJ, Hamilton J, Reese K, Sillo GR, Stabile PQ, Sterling RC. Is exposure to an effective contingency management intervention associated with more positive provider beliefs? J Subst Abuse Treat. 2012 Jun; 42(4): 356-365

Brief Intervention for Drug-Abusing Adolescents in a School Setting: Outcomes and Mediating Factors This randomized controlled trial evaluated the use of two brief intervention conditions for adolescents (aged 12-18 years) who have been identified in a school setting as abusing alcohol and other drugs. Adolescents and their parents (N = 315) were randomly assigned to receive either a two-session adolescent-only (BI-A), two-session adolescent and additional parent session (BI-AP), or assessment-only control condition (CON). Interventions were manually guided and delivered in a school setting by trained counselors. Adolescents and parents were assessed at intake and at 6 months following the completion of the intervention. Analyses of relative (change from intake to 6 months) and absolute (status at 6 months) outcome variables indicated that for the most part, adolescents in the BI-A and BI-AP conditions showed significantly more reductions in drug use behaviors compared with the CON group. In addition, youth receiving the BI-AP condition

showed significantly better outcomes compared with the BI-A group on several variables. Problem-solving skills and use of additional counseling services mediated outcome. The value of a school-based brief intervention for students is discussed. Winters KC, Fahnhorst T, Botzet A, Lee S, Lalone B. Brief intervention for drug-abusing adolescents in a school setting: outcomes and mediating factors. J Subst Abuse Treat. 2012 Apr; 42(3): 279-288.

Experiences Associated with Intervening with Homeless, Substance-Abusing Mothers: The Importance of Success This article documents the experiences of providing housing and supportive services, or ecologically based treatment, to shelter-recruited, substance-abusing homeless women with young children in their care. Among clients, observed experiences related to housing, substance abuse, and health and mental health care are discussed. Among therapists, experiences related to managing the chaotic nature of the client's lives, wanting to manage the client's lives, and frustration with client's life trajectories are reviewed. Observations related to the therapeutic process include the client's relationship to the therapist, balancing the client's independence and need for assistance, and unrealistic expectations among the clients. Recommendations for successfully approaching these clinical situations and experiences are offered. The purpose of this article is to document these therapy experiences to facilitate the work of future teams seeking to intervene in the lives of homeless families through homeless shelters or other settings. Slesnick N, Glassman M, Katafiasz H, Collins JC. Experiences associated with intervening with homeless, substance-abusing mothers: the importance of success. Soc Work. 2012 Oct; 57(4): 343-352.

Comparing Culturally Accommodated Versus Standard Group CBT for Latino Adolescents with Substance Use Disorders: A Pilot Study Studies comparing empirically supported substance abuse treatments versus their culturally accommodated counterparts with participants from a specific ethnic minority group are lacking in the literature. To address this gap, this pilot study was conducted to compare the feasibility and relative efficacy of an empirically supported standard version of cognitive-behavioral substance abuse treatment (S-CBT) to a culturally accommodated version (A-CBT) with a sample of Latino adolescents. This study was guided by a Cultural Accommodation Model for Substance Abuse Treatment (CAM-SAT). Thirty-five Latino adolescents (mean age = 15.49) were randomly assigned to one of two 12-week group-based treatment conditions (S-CBT = 18; A-CBT = 17) with assessments conducted at pretreatment, posttreatment and 3-month follow-up. Results indicated similar retention and satisfaction rates for participants in both treatment conditions. In addition, participants in both conditions demonstrated significant decreases in substance use from pre- to posttreatment with slight increases at 3-month follow-up; however, substance use outcomes were moderated by two cultural variables: ethnic identity and familism. Implications of these findings within the context of conducting clinical trials with Latino adolescents are discussed. Burrow-Sanchez JJ, Wrona M. Comparing culturally accommodated versus standard group CBT for Latino adolescents with substance use disorders: a pilot study. Cultur Divers Ethnic Minor Psychol. 2012 Oct; 18(4): 373-383.

Empirically Supported Family-Based Treatments for Conduct Disorder and Delinquency in Adolescents Several family-based treatments of conduct disorder and delinquency in adolescents have emerged as evidence-based and, in recent years, have been transported to more than 800 community practice settings. These models include multisystemic therapy, functional family therapy, multidimensional treatment foster care, and, to a lesser extent, brief strategic family therapy. In addition to summarizing the theoretical and clinical bases of these treatments, their results in efficacy and effectiveness trials are examined with particular emphasis on any

demonstrated capacity to achieve favorable outcomes when implemented by real-world practitioners in community practice settings. Special attention is also devoted to research on purported mechanisms of change as well as the long-term sustainability of outcomes achieved by these treatment models. Importantly, the authors note that the developers of each of the models have developed quality assurance systems to support treatment fidelity and youth and family outcomes; and the developers have formed purveyor organizations to facilitate the large-scale transport of their respective treatments to community settings nationally and internationally. Henggeler SW, Sheidow AJ. Empirically supported family-based treatments for conduct disorder and delinquency in adolescents. J Marital Fam Ther. 2012 Jan; 38(1): 30-58.

Drug Use and HIV Risk Outcomes in Opioid-Injecting Men in the Republic of Georgia: Behavioral Treatment + Naltrexone Compared to Usual Care To test the initial feasibility of a novel 22-week comprehensive intervention pairing behavioral treatment with naltrexone that aimed at engaging, retaining, and treating opioid-injecting men in the Republic of Georgia. Forty opioid-injecting male and their drug-free female partners participated in a two-group randomized clinical trial at the field site of the Union Alternative Georgia, in Tbilisi, Republic of Georgia. The comprehensive intervention that paired behavioral treatment with naltrexone for the male participants (n=20) included counseling sessions using Motivational Interviewing for both the male participant and the couple, monetary incentives for drug abstinence, and research-supported detoxification followed by naltrexone treatment. Male participants in the usual care condition (n=20) had the opportunity to attend once-a-week individualized education sessions and upon request receive referrals to detoxification programs and aftercare that could or could not have included naltrexone. Outcome measures included entry into inpatient detoxification and naltrexone treatment, urine drug screening, reduction in illicit substance use, use of benzodiazepines, injection of buprenorphine, and needle and syringe sharing. The comprehensive intervention condition showed significantly more weekly urine samples negative for illicit opioids during weeks 1-22 (7.0 vs. 1.4; $p<.001$) and reported significant declines in use of benzodiazepines and injection of buprenorphine (both $ps<.004$). The first behavioral treatment randomized clinical trial in the Republic of Georgia found that the use of tailored behavioral therapy paired with naltrexone is both feasible and efficacious for treating drug use and reducing HIV drug-risk behavior in Georgian men. Otiashvili D, Kirtadze I, O'Grady KE, Jones HE. Drug use and HIV risk outcomes in opioid-injecting men in the Republic of Georgia: behavioral treatment + naltrexone compared to usual care. Drug Alcohol Depend. 2012 Jan 1; 120(1-3): 14-21.

Cognitive Neurorehabilitation of HIV-associated Neurocognitive Disorders: A Qualitative Review and Call to Action Despite significant advances in the virologic management of HIV infection over the last two decades, effective treatments for HIV-associated neurocognitive disorders (HAND) remain elusive. While pharmacological interventions have yielded some success in improving neurocognitive outcomes in HIV, there is a dearth of rigorous studies examining the efficacy of cognitive rehabilitation for remediating HIV-associated neurocognitive impairment. This qualitative review summarizes and critiques the emerging literature on cognitive and behavioral treatments for HAND, which provides many reasons for optimism, but also has major limitations that underscore the scope of the work that lies ahead. Considering the notable real-world consequences of HAND, the development, validation, and clinical deployment of cognitive neurorehabilitation interventions tailored to the needs of persons living with HIV infection is a priority for clinical neuroAIDS investigators. In describing potential future directions for this endeavor, particular attention was paid to the application of cognitive neuropsychological principles in developing theory-driven approaches to managing HAND, improving everyday functioning, and

enhancing HIV health outcomes. Weber E, Blackstone K, Woods SP. Cognitive neurorehabilitation of HIV-associated neurocognitive disorders: A qualitative review and call to action. Neuropsychol Rev. 2013 Feb 16. [Epub ahead of print].

Leveraging Technology to Enhance Addiction Treatment and Recovery Technology such as the Internet and mobile phones offers considerable promise for affecting the assessment, prevention, and treatment of and recovery from substance use disorders. Technology may enable entirely new models of behavioral health care within and outside of formal systems of care. This article reviews the promise of technology-based therapeutic tools for affecting the quality and reach of addiction treatment and recovery support systems, as well as the empirical support to date for this approach. Potential models for implementing technology-based interventions targeting substance use disorders are described. Opportunities to optimize the effectiveness and impact of technology-based interventions targeting addiction and recovery, along with outstanding research needs, are discussed. Marsch LA. Leveraging technology to enhance addiction treatment and recovery. J Addict Dis. 2012; 31(3): 313-318.

The Co-Occurring Use and Misuse of Cannabis and Tobacco: A Review Cannabis and tobacco use and misuse frequently co-occur. This review examines the epidemiological evidence supporting the life-time co-occurrence of cannabis and tobacco use and outlines the mechanisms that link these drugs to each other. Mechanisms include (i) shared genetic factors; (ii) shared environmental influences, including (iii) route of administration (via smoking), (iv) co-administration and (v) models of co-use. We also discuss respiratory harms associated with co-use of cannabis and tobacco, overlapping withdrawal syndromes and outline treatment implications for co-occurring use. Findings are based on a selective review of published studies. Both cannabis and tobacco use and misuse are influenced by genetic factors, and a proportion of these genetic factors influence both cannabis and tobacco use and misuse. Environmental factors such as availability play an important role, with economic models suggesting a complementary relationship where increases in price of one drug decrease the use of the other. Route of administration and smoking cues may contribute to their sustained use. Similar withdrawal syndromes, with many symptoms in common, may have important treatment implications. Emerging evidence suggests that dual abstinence may predict better cessation outcomes, yet empirically researched treatments tailored for co-occurring use are lacking. In conclusion, there is accumulating evidence that some mechanisms linking cannabis and tobacco use are distinct from those contributing to co-occurring use of drugs in general. There is an urgent need for research to identify the underlying mechanisms and harness their potential etiological implications to tailor treatment options for this serious public health challenge. Agrawal A, Budney AJ, Lynskey MT. The co-occurring use and misuse of cannabis and tobacco: a review. Addiction. 2012 Jul; 107(7): 1221-1233.

Quantifying the Clinical Significance of Cannabis Withdrawal Questions over the clinical significance of cannabis withdrawal have hindered its inclusion as discrete cannabis induced psychiatric condition in the Diagnostic and Statistical Manual of Mental Disorders (DSM IV). This study aims to quantify functional impairment to normal daily activities from cannabis withdrawal, and looks at the factors predicting functional impairment. In addition, the study tests the influence of functional impairment from cannabis withdrawal on cannabis use during and after an abstinence attempt. A volunteer sample of 49 non-treatment seeking cannabis users who met DSM-IV criteria for dependence provided daily withdrawal-related functional impairment scores during a one-week baseline phase and two weeks of monitored abstinence from cannabis with a one month follow up. Functional impairment from withdrawal symptoms was strongly associated with symptom severity

(p=0.0001). Participants with more severe cannabis dependence before the abstinence attempt reported greater functional impairment from cannabis withdrawal (p=0.03). Relapse to cannabis use during the abstinence period was associated with greater functional impairment from a subset of withdrawal symptoms in high dependence users. Higher levels of functional impairment during the abstinence attempt predicted higher levels of cannabis use at one month follow up (p=0.001). Cannabis withdrawal is clinically significant because it is associated with functional impairment to normal daily activities, as well as relapse to cannabis use. Sample size in the relapse group was small and the use of a non-treatment seeking population requires findings to be replicated in clinical samples. Tailoring treatments to target withdrawal symptoms contributing to functional impairment during a quit attempt may improve treatment outcomes. Allsop DJ, Copeland J, Norberg MM, Fu S, Molnar A, Lewis J, Budney AJ. Quantifying the clinical significance of cannabis withdrawal. PLoS One. 2012; 7(9): e44864.

Initiation of Abstinence in Adolescents Treated for Marijuana Use Disorders This study assessed the time to initiation of marijuana abstinence in an adolescent treatment-seeking sample, and identified variables that were predictive of abstinence. Adolescents (N=69), ages 14 to 18 were randomly assigned to one of two 14-week behavioral treatments. Abstinence was measured with twice-weekly urine toxicology plus teen and parent reports. Discrete-time survival and hazard functions were conducted. The majority of adolescents achieved at least 1week of abstinence, and 51% achieved 6weeks of abstinence. Initiation of abstinence occurred by the sixth treatment week for 94% of teens with any abstinence suggesting that alternative, clinical approaches should be considered for those not responding by week 6. Teens with a drug negative urinalysis at intake, and teens that had two parents participating in treatment were more likely to achieve at least 6 weeks of abstinence. These findings, if replicated, can be used to inform clinical and research strategies that might lead to enhanced treatment efficacy and cost effectiveness for substance abuse treatment programming. Brown PC, Budney AJ, Thostenson JD, Stanger C. Initiation of abstinence in adolescents treated for marijuana use disorders. J Subst Abuse Treat. 2013 Apr; 44(4): 384-390.

The Impact of Disruptive Behavior Disorder on Substance Use Treatment Outcome in Adolescents The current study examined the impact of disruptive behavior disorder (DBD) on substance use outcomes in an adolescent sample. Sixty-eight adolescents and their caregivers were randomized to one of two fourteen-week, outpatient treatments: Motivational Enhancement Therapy/Cognitive Behavior Therapy (MET/CBT)+Parent Management Training+Contingency Management (CM; experimental) and MET/CBT+Parent Drug Education (attention control). This study assessed abstinence, substance use, externalizing behavior, and parenting outcomes over five assessment periods for youth with DBD (DBD(+)) and without DBD (DBD(-)). Results showed DBD(+)/experimental adolescents reported fewer days of marijuana use than DBD(+)/control adolescents. Results also showed that parents of DBD(-) adolescents in the experimental condition reported significantly better parenting outcomes compared to DBD(-)/control. Substance abuse treatment for adolescents with DBD which includes a component such as contingency management and parent training has the potential to contribute to substance use outcomes. Such treatment strategies, however, should include additional support for parents. Ryan SR, Stanger C, Thostenson J, Whitmore JJ, Budney AJ. The impact of disruptive behavior disorder on substance use treatment outcome in adolescents. J Subst Abuse Treat. 2012 Dec 7. pii: S0740-5472(12)00425-4. [Epub ahead of print].

Reducing Substance Use Risk and Mental Health Problems among Sexually Assaulted Adolescents: A Pilot Randomized Controlled Trial The current study reports results from a pilot randomized controlled trial evaluating the feasibility and efficacy of Risk Reduction through Family Therapy (RRFT) for reducing substance use risk and trauma-related mental health problems among sexually assaulted adolescents. Thirty adolescents (aged 13-17 years; M = 14.80; SD = 1.51) who had experienced at least one sexual assault and their caregivers were randomized to RRFT or treatment as usual (TAU) conditions. Participants completed measures of substance use, substance use risk factors (e.g., family functioning), mental health problems (i.e., posttraumatic stress disorder, depression, and general internalizing/externalizing symptoms) and risky sexual behavior at four time points (baseline, posttreatment, and 3- and 6-month follow-up). Mixed-effects regression models yielded significantly greater reductions in substance use, specific substance use risk factors, and (parent-reported) PTSD, depression, and general internalizing symptoms among youth in the RRFT condition relative to youth in the TAU condition. However, significant baseline differences in functioning between the two conditions warrant caution in interpreting between-groups findings. Instead, emphasis is placed on replication of feasibility findings and within-group improvements over time among the RRFT youth. Danielson CK, McCart MR, Walsh K, de Arellano MA, White D, Resnick HS. Reducing substance use risk and mental health problems among sexually assaulted adolescents: a pilot randomized controlled trial. J Fam Psychol. 2012 Aug; 26(4): 628-635.

Peritraumatic Dissociation and Peritraumatic Emotional Predictors of PTSD in Latino Youth: Results from the Hispanic Family Study This is the 1st study to examine peritraumatic dissociation and peritraumatic emotions as they predict symptoms and diagnosis of posttraumatic stress disorder (PTSD) in Latino youth. The authors' aim was to test the hypothesis that the degree of peritraumatic dissociation would predict the number of PTSD symptoms and PTSD clinical diagnosis when the influences of other salient factors were statistically controlled. They also explored the possible contributions of peritraumatic emotional responses to PTSD symptomatology and PTSD diagnosis. They expected that peritraumatic dissociation would emerge as a significant predictor of PTSD. A total of 204 Latino youth (mean age = 12.37 years) completed semistructured individual clinical interviews with bilingual research assistants. These interviews assessed trauma exposure, peritraumatic responses, and current psychopathology. A linear regression analysis demonstrated significant relationships between lifetime number of traumatic events, peritraumatic dissociation, shame, and number of PTSD symptoms endorsed. Significant inverse (protective) relationships were demonstrated between anger and guilt and current PTSD symptomatology. Logistic regression analysis demonstrated significant relationships between peritraumatic dissociation, shame, lifetime number of traumatic events experienced, and PTSD diagnosis. The analyses examined both the number of PTSD symptoms as well as diagnosis of PTSD while simultaneously controlling for age, lifetime exposure to traumatic events, time residing in the United States, and gender. These results support an increasingly robust body of empirical literature suggesting that the peritraumatic dissociative and emotional responses to trauma are important predictors of future PTSD diagnosis. Possible cultural factors contributing to the dissociative responses in Latino youth and clinical implications are discussed. Vásquez DA, de Arellano MA, Reid-Quiñones K, Bridges AJ, Rheingold AA, Stocker RP, Danielson CK. Peritraumatic dissociation and peritraumatic emotional predictors of PTSD in Latino youth: results from the Hispanic family study. Trauma Dissociation. 2012; 13(5): 509-525.

Substance-Abusing Mothers in Residential Treatment with their Babies: Importance of Pre- and Postnatal Maternal Reflective Functioning A residential treatment program has been developed specifically for substance-abusing pregnant and parenting women in Finland, focusing on simultaneously supporting maternal abstinence from substances and the mother-baby relationship. The aims of the study are to explore maternal pre- and postnatal reflective functioning and its association with background factors, maternal exposure to trauma, and psychiatric symptoms, postnatal interaction, child development, and later child foster care placement. Participants were 34 mother-baby pairs living in three residential program units during the pre- to postnatal period. The authors employed self-report questionnaires on background, trauma history, and psychiatric symptoms (Brief Symptom Inventory: L.R. Derogatis, 1993; Edinburgh Postnatal Depression Scale: J.L. Cox, J.M. Holden, & R. Sagovsky, 1987; Traumatic Antecedents Questionnaire: B. Van der Kolk, 2003), videotaped mother-child interactions coded for sensitivity, control, and unresponsiveness (Care Index for Infants and Toddlers: P. Crittenden, 2003); a standardized test of child development (Bayley Scales of Infant Development-II: N. Bayley, 1993); and semistructured interviews for maternal reflective functioning (Pregnancy Interview: A. Slade, E. Bernbach, J. Grienenberger, D.W. Levy, & A. Locker, 2002; Parent Development Interview: A. Slade et al., 2005). Pre- and postnatal maternal reflective functioning (RF) was on average low, but varied considerably across participants. Average RF increased significantly during the intervention. Increase in RF level was found to be associated with type of abused substance and maternal trauma history. Mothers who showed lower postnatal RF levels relapsed to substance use more often after completing a residential treatment period, and their children were more likely to be placed in foster care. The intensive focus on maternal RF is an important direction in the development of efficacious treatment for this very high risk population. Pajulo M, Pyykkönen N, Kalland M, Sinkkonen J, Helenius H, Punamäki RL, Suchman N. Substance-abusing mothers in residential treatment with their babies: importance of pre- and postnatal maternal reflective functioning. Infant Ment Health J. 2012 Jan; 33(1): 70-81.

Sensation Seeking, Coping with Stress, and Readiness to Engage in Therapy: Does Ego Development Influence the Psychosocial Functioning of Substance-Abusing Mothers? Ego development, the capacity to derive coherent, nuanced meaning from one's life experiences, often has significant impact on psychosocial adjustment during adulthood. Research with nonclinical populations has indicated links between higher ego development and healthy emotional coping and interpersonal relationships. Emerging research with substance-abusing mothers suggests that higher levels of ego development are associated with improved parenting but also with increased rates of psychopathology. Less is known about how ego development is related to other psychosocial factors important for substance-abusing mothers' functioning and capacity to parent, including the proclivity to engage in risky behaviors, adaptive coping behaviors, and readiness to engage in psychotherapy. The present study examines these links. Participants included 182 methadone maintained women who expressed interest in a randomized clinical trial testing the efficacy of a relational parenting intervention for substance-abusing mothers (Luthar, Suchman, & Altomare, 2007). Data were analyzed using a series of MANCOVAs and ANCOVAs controlling for maternal IQ and depression. Mothers with higher levels of ego development reported more adaptive coping techniques and greater readiness to engage in psychotherapy but also reported a heightened desire for strong sensations. Findings are discussed in light of mothers' psychological processes and parenting capacities. The significance of findings for developing parenting interventions for substance-abusing mothers is also discussed. David DH, McMahon TJ, Luthar SL, Suchman NE. Sensation seeking, coping with stress, and readiness to engage in therapy: Does ego development

influence the psychosocial functioning of substance-abusing mothers? Am J Orthopsychiatry. 2012 Apr; 82(2): 231-240.

A Randomized Trial of Cognitive Behavioral Therapy in Primary Care-Based Buprenorphine The objective of this study was to determine the impact of cognitive behavioral therapy on outcomes in primary care, office-based buprenorphine/naloxone treatment of opioid dependence. The authors conducted a 24-week randomized clinical trial in 141 opioid-dependent patients in a primary care clinic. Patients were randomized to physician management or physician management plus cognitive behavioral therapy. Physician management was brief, manual guided, and medically focused; cognitive behavioral therapy was manual guided and provided for the first 12 weeks of treatment. The primary outcome measures were self-reported frequency of illicit opioid use and the maximum number of consecutive weeks of abstinence from illicit opioids, as documented by urine toxicology and self-report. Results indicated that the 2 treatments had similar effectiveness with respect to reduction in the mean self-reported frequency of opioid use, from 5.3 days per week (95% confidence interval, 5.1-5.5) at baseline to 0.4 (95% confidence interval, 0.1-0.6) for the second half of maintenance (P<.001 for the comparisons of induction and maintenance with baseline), with no differences between the 2 groups (P=.96) or between the treatments over time (P=.44). For the maximum consecutive weeks of opioid abstinence there was a significant main effect of time (P<.001), but the interaction (P=.11) and main effect of group (P=.84) were not significant. No differences were observed on the basis of treatment assignment with respect to cocaine use or study completion. The authors conclude that among patients receiving buprenorphine/naloxone in primary care for opioid dependence, the effectiveness of physician management did not differ significantly from that of physician management plus cognitive behavioral therapy. Fiellin DA, Barry DT, Sullivan LE, Cutter CJ, Moore BA, O'Connor PG, Schottenfeld RS. A randomized trial of cognitive behavioral therapy in primary care-based buprenorphine. Am J Med. 2013 Jan; 126(1): 74.e11-7. doi: 10.1016/j.amjmed.2012.07.005. [Epub ahead of print].

The Recovery Line: A Pilot Trial of Automated, Telephone-Based Treatment for Continued Drug Use in Methadone Maintenance The current pilot study evaluated feasibility, acceptability, and initial efficacy of a therapeutic Interactive Voice Response (IVR) system ("the Recovery Line") for patients receiving methadone maintenance who continue to use illicit drugs. Patients were randomized (N=36) to 4weeks of treatment-as-usual (TAU) or Recovery Line plus TAU. Ratings of the Recovery Line were high and remained stable throughout the study. However, despite instructions and reminders, patients used substantially less than the recommended daily use (<10days of 28). Patients were more likely to report abstinence from opioids and cocaine on days they used the Recovery Line (p=.01) than those they did not. Conditions did not differ significantly on patient satisfaction, urine screen outcomes, or coping efficacy. As with other computer-based treatments, findings suggest the Recovery Line is acceptable and feasible. However, additional methods to increase patient utilization of automated systems and larger clinical trials are needed. Moore BA, Fazzino T, Barry DT, Fiellin DA, Cutter CJ, Schottenfeld RS, Ball SA. The Recovery Line: A pilot trial of automated, telephone-based treatment for continued drug use in methadone maintenance. J Subst Abuse Treat. 2013 Jan 29. pii: S0740-5472(12)00472-2. doi: 10.1016/j.jsat.2012.12.011. [Epub ahead of print].

HealthCall: Technology-Based Extension of Motivational Interviewing to Reduce Non-injection Drug Use in HIV Primary Care Patients - A Pilot Study To reduce non-injection drug use (NIDU) among HIV primary care patients, more than a single brief intervention may be needed, but clinic resources are often too limited for extended interventions. To extend brief motivational interviewing (MI) to reduce NIDU, the authors designed and conducted a pilot study of "HealthCall," consisting of brief (1-3 minutes) daily patient calls reporting NIDU and health behaviors to a telephone-based interactive voice response (IVR) system, which provided data for subsequent personalized feedback. Urban HIV adult clinic patients reporting ≥4 days of NIDU in the previous month were randomized to two groups: MI-only (n=20) and MI+HealthCall (n=20). At 30 and 60 days, patients were assessed and briefly discussed their NIDU behaviors with their counselors. The outcome was the number of days patients used their primary drug in the prior 30 days. Medical marijuana issues precluded HealthCall with patients whose primary substance was marijuana (n=7); excluding these, 33 remained, of whom 28 patients (MI-only n=17; MI+HealthCall n=11) provided post-treatment data for analysis. Time significantly predicted reduction in "days used" in both groups ($p<0.0001$). At 60 days, between-group differences approached trend level, with an effect size of 0.62 favoring the MI+HealthCall arm. This pilot study suggests that HealthCall is feasible and acceptable to patients in resource-limited HIV primary care settings and can extend patient involvement in brief intervention with little additional staff time. A larger efficacy trial of HealthCall for NIDU-reduction in such settings is warranted. Aharonovich E, Greenstein E, O'Leary A, Johnston B, Seol SG, Hasin DS. HealthCall: technology-based extension of motivational interviewing to reduce non-injection drug use in HIV primary care patients - a pilot study. AIDS Care. 2012; 24(12): 1461-1469. doi: 10.1080/09540121. 2012.663882. 2012 Mar 20. [Epub ahead of print].

Interventions to Address Chronic Disease and HIV: Strategies to Promote Smoking Cessation Among HIV-infected Individuals Tobacco use, especially cigarette smoking, is higher than average in persons living with HIV/AIDS (PLWHA). The Public Health Service Clinical Practice Guideline for Treating Tobacco Use and Dependence states that, during every medical encounter, all smokers should be offered smoking cessation counseling, along with approved medications. The Guideline also recognizes PLWHA as a priority population, given the scarcity of research on effective cessation treatments in this group. The scant evidence suggests that conventional treatments, though worthwhile, are not as successful as might be hoped for. The reasons for this are not entirely clear, but may have to do with the complex array of medical and psychosocial factors that complicate their lives. Clinicians should consider re-treatment strategies for those patients who encounter difficulty when quitting smoking with conventional approaches, switching or augmenting treatments as needed to minimize adverse experiences, and to maximize tolerability, adherence, and cessation outcomes. Niaura R, Chander G, Hutton H, Stanton C. Interventions to address chronic disease and HIV: strategies to promote smoking cessation among HIV-infected individuals. Curr HIV/AIDS Rep. 2012 Dec; 9(4): 375-384.

Moderating Effects of Race in Clinical Trial Participation and Outcomes Among Marijuana-Dependent Young Adults Few studies have examined clinical trial participation rates and treatment outcomes among underserved young adults who are dependent on marijuana, the most commonly abused illicit drug. The present study was a secondary analysis of a trial of court-referred marijuana-dependent young adults (ages 18-25) randomized to one of four treatment conditions: Motivational Enhancement Therapy/Cognitive Behavioral Therapy (MET/CBT), MET/CBT+Contingency Management (CM), Drug Counseling (DC) or DC+CM. African American (N=81) participants were compared to White (N=31) participants with respect to rates of

participation in phases of treatment and substance use outcomes. In addition, the interaction of race and treatment condition was examined to ascertain if the interventions yielded different effects based on race. Among those who started treatment, African American young adults were significantly less likely to complete the treatment and posttreatment phases of the clinical trial than their White counterparts. Irrespective of treatment type, substance use outcomes (i.e., percentage of marijuana-negative specimens and longest duration of continuous abstinence) did not vary by race. However, there was a significant interaction effect between treatment type and race; African American young adults did not benefit differentially from any specific type of treatment, but CM was effective in reducing proportion of marijuana positive samples among White young adults. Findings suggest that clinical trial treatment and posttreatment completion rates vary by race in this population, as does response to specific treatment types. More treatment research focusing specifically on African American marijuana-dependent young adults is warranted. Montgomery L, Petry NM, Carroll KM. Moderating effects of race in clinical trial participation and outcomes among marijuana-dependent young adults. Drug Alcohol Depend. 2012 Dec 1; 126(3): 333-339.

Smoking Cessation Interventions with Female Smokers Living with HIV/AIDS: A Randomized Pilot Study of Motivational Interviewing Smoking among people living with HIV, particularly women living with HIV, is associated with higher morbidity and mortality rates when compared to nonsmoking individuals with HIV. Despite patients' higher risk of adverse health outcomes, in particular preventable smoking-related diseases for smokers living with HIV, few smoking cessation interventions have been examined with this population. The aim of the current study was to test the potential efficacy of a brief motivational intervention for smoking cessation with HIV-infected women smokers. Participants (N=30) were randomly assigned to receive a single session of motivational interviewing (MI) or prescribed advice (PA). The primary outcome was seven-day point prevalence abstinence at the one-month follow-up interview. Secondary outcome measures included mean cigarettes smoked per day, desire to quit smoking, perceived difficulty in quitting smoking, and expectation of success. The authors detected no significant differences between intervention and control groups in self-reported seven-day point prevalence abstinence at the one-month follow-up. However, participants in the MI condition reported a significant decrease in the mean cigarettes smoked per day when compared to the PA condition. There were no significant between-group differences in participants' desire to quit, perceived difficulty, and expectation of success. The results of this pilot study indicate that MI may be an effective smoking cessation intervention for HIV-positive women smokers and should be studied further in a larger clinical trial. Manuel JK, Lum PJ, Hengl NS, Sorensen JL. Smoking cessation interventions with female smokers living with HIV/AIDS: A randomized pilot study of motivational interviewing. AIDS Care. 2012 Nov 2. [Epub ahead of print].

Possible Barriers to Enrollment in Substance Abuse Treatment Among a Diverse Sample of Asian Americans and Pacific Islanders: Opinions of Treatment Clients This mixed methods study examined motivations and barriers to substance abuse treatment entry and treatment continuation among Asian American and Pacific Islander (AAPI) substance users. AAPI substance users (N = 61) were recruited from substance abuse treatment programs in California and Hawaii. Semi-structured interviews and interviewer-administered surveys assessed barriers and facilitators to entering substance abuse treatment. Barriers included peer pressure, family influences, and face loss concerns. Facilitators included peer support, involvement in the criminal justice system, a perceived need for treatment, and culturally competent substance abuse treatment services. Family and peer influences may act as both facilitators and impediments. AAPI substance using populations face many of the same individual-level and structural and systems barriers to entry to

treatment as other substance using populations. However, similar to other racial/ethnic minority groups, it is important to address cultural differences and develop culturally competent substance abuse treatments for the AAPI population. Masson CL, Shopshire MS, Sen S, Hoffman KA, Hengl NS, Bartolome J, McCarty D, Sorensen JL, Iguchi MY. Possible barriers to enrollment in substance abuse treatment among a diverse sample of Asian Americans and Pacific Islanders: opinions of treatment clients. J Subst Abuse Treat. 2013 Mar; 44(3): 309-315.

Directly Administered Antiretroviral Therapy: Pilot Study of a Structural Intervention in Methadone Maintenance Devising interventions to provide integrated treatment for addiction and medical problems is an urgent issue. This study piloted a structural intervention, Directly Administered Antiretroviral Therapy (DAART), to assist methadone-maintenance patients in HIV medication adherence. Twenty-four participants received: (1) antiretroviral medications at the methadone clinic daily before receiving their methadone; (2) take-home antiretroviral medication for days they were not scheduled to attend the methadone clinic, and (3) brief adherence counseling to address adherence barriers. DAART lasted 24 weeks, with a planned step-down to twice-weekly administration in weeks 25-36, followed by self-administration in weeks 37-48. Retention rates at weeks 24, 36, and 48 were 83, 92, and 75% respectively. DAART was associated with improvement in the proportion of participants achieving viral suppression as well as with high medication adherence rates (clinic-verified; 85% and self-reported 97%) during the active intervention phase. DAART was effective as an intervention but did not promote transition to self-administration. This study demonstrates that DAART is adaptable and simple enough to be implemented into methadone treatment programs interested in providing HIV adherence services. Sorensen JL, Haug NA, Larios S, Gruber VA, Tulsky J, Powelson E, Logan DP, Shapiro B. Directly administered antiretroviral therapy: pilot study of a structural intervention in methadone maintenance. J Subst Abuse Treat. 2012 Dec; 43(4): 418-423.

Predictors of Stimulant Abuse Treatment Outcomes in Severely Mentally Ill Outpatients Severe mental illness is often exclusionary criteria for studies examining factors that influence addiction treatment outcome. Therefore, little is known about predictors of treatment response of individuals receiving psychosocial treatments for addictions who suffer from co-occurring severe mental illness. The impact of demographic, substance abuse severity, psychiatric severity, and service utilization variables on in-treatment performance (i.e., longest duration of abstinence) in a 12-week contingency management (CM) intervention for stimulant abuse in 96 severely mentally ill adults was investigated. A 4-step linear regression was used to identify independent predictors of in-treatment abstinence. This model accounted for 37.4% of variance in the longest duration of abstinence outcome. Lower levels of stimulant use (i.e., stimulant-negative urine test) and psychiatric severity (i.e., lower levels of psychiatric distress), as well as higher rates of outpatient treatment utilization at study entry were independently associated with longer duration of drug abstinence. These data suggest that individuals with low levels of stimulant use and psychiatric severity, as well as those actively engaged in services are most likely to succeed in a typical CM intervention. For others, modifications to CM interventions, such as increasing the value of reinforcement or adding CM to evidence based psychiatric interventions may improve treatment outcomes. Angelo FN, McDonell MG, Lewin MR, Srebnik D, Lowe J, Roll J, Ries R. Predictors of stimulant abuse treatment outcomes in severely mentally ill outpatients. Drug Alcohol Depend. 2012 Dec 26. pii: S0376-8716(12)00458-9. doi: 10.1016/j.drugalcdep.2012.11.017. [Epub ahead of print].

Randomized Controlled Trial of Contingency Management for Stimulant Use in Community Mental Health Patients with Serious Mental Illness The primary objective of this study was to determine whether contingency management was associated with increased abstinence from stimulant drug use in stimulant-dependent patients with serious mental illness treated in a community mental health center. Secondary objectives were to determine whether contingency management was associated with reductions in use of other substances, psychiatric symptoms, HIV risk behavior, and inpatient service utilization. A randomized controlled design was used to compare outcomes of 176 outpatients with serious mental illness and stimulant dependence. Participants were randomly assigned to receive 3 months of contingency management for stimulant abstinence plus treatment as usual or treatment as usual with reinforcement for study participation only. Urine drug tests and self report, clinician-report, and service utilization outcomes were assessed during the 3-month treatment period and the 3-month follow-up period. Although participants in the contingency management condition were significantly less likely to complete the treatment period than those assigned to the control condition (42% compared with 65%), they were 2.4 times (95% CI=1.9–3.0) more likely to submit a stimulant-negative urine test during treatment. Compared with participants in the control condition, they had significantly lower levels of alcohol use, injection drug use, and psychiatric symptoms and were one-fifth as likely as those assigned to the control condition to be admitted for psychiatric hospitalization during treatment. They also reported significantly fewer days of stimulant drug use during the 3-month follow-up. When added to treatment as usual, contingency management is associated with large reductions in stimulant, injection drug, and alcohol use. Reductions in psychiatric symptoms and hospitalizations are important secondary benefits. McDonell MG, Srebnik D, Angelo F, McPherson S, Lowe JM, Sugar A, Short RA, Roll JM, Ries RK. Randomized controlled trial of contingency management for stimulant use in community mental health patients with serious mental illness. Am J Psychiatry. 2013 Jan 1; 170(1): 94-101.

Preventing Addiction Related Suicide: A Pilot Study Persons addicted to alcohol and drugs are at 5-10 times higher risk for suicide as compared to the general population. To address the need for improved suicide prevention strategies in this population, the Preventing Addiction Related Suicide (PARS) module was developed. Pilot testing of 78 patients demonstrated significant post-treatment changes in knowledge [$t(66)=12.07$, $p=.000$] and attitudes [$t(75)=6.82$, $p=.000$] toward suicide prevention issues. Significant gains were maintained at 1-month follow-up for changes in knowledge [$t(55)=6.33$, $p=.000$] and attitudes [$t(61)=3.37$, $p=.0001$], with changes in positive help seeking behaviors in dealing with suicidal issues in friends [$\chi(2)(1) =10.49$, $p=.007$], family [$\chi(2)(1)=9.81$, $p=.015$], and self [$\chi(2)(1)=19.62$, $p=.008$] also observed. The PARS was also highly rated by treatment staff as feasible within their standard clinical practice. Voss WD, Kaufman E, O'Connor SS, Comtois KA, Conner KR, Ries RK. Preventing addiction related suicide: A pilot study. J Subst Abuse Treat. 2013 Jan 31. pii: S0740-5472(12)00422-9. doi: 10.1016/j.jsat.2012.10.006. [Epub ahead of print].

Perceived Partner Responsiveness Predicts Decreases in Smoking over the First Nine Years of Marriage Support for quitting is associated with smoking cessation, but few studies have examined the influence of more general social support on smoking outcomes. The current research examines perceptions of the partner's willingness and ability to provide general social support (i.e., perceived partner responsiveness) as a longitudinal predictor of smoking trajectories. Data are from a sample of newlywed couples assessed at six time points over 9 years. The current analyses focus on both partners in 333 "ever-smoker" couples. Participants completed measures of partner responsiveness, smoking, and demographics through the mail at each time point. Both husbands

and wives who initially reported greater partner responsiveness showed a decrease over the following 9 years in the likelihood of being a smoker and in cigarette quantity. This decrease was not apparent for husbands and wives who initially reported lower partner responsiveness. These effects were mediated by several time-varying characteristics. Previous research has shown that support for quitting is an important predictor of smoking cessation. The current research demonstrates that more general perceived social support, unrelated to smoking behavior, also predicts decreases in smoking over time in both men and women. In fact, reports of partner responsiveness at baseline predicted smoking over 9 years, demonstrating the potency of this particular relationship perception for smoking outcomes. Derrick JL, Leonard KE, Homish GG. Perceived partner responsiveness predicts decreases in smoking over the first nine years of marriage. Nicotine Tob Res. 2013 Feb 18. [Epub ahead of print].

An Ecological Momentary Assessment Analysis of Prequit Markers for Smoking-Cessation Failure This study aimed to identify correlates of smoking-cessation failure, a failure to establish abstinence during a quit-smoking attempt. Identifying risk factors for early failure could facilitate the development of tailored interventions to promote cessation. The current study used existing ecological momentary assessment (EMA) data to investigate the extent to which prequit craving, negative affect, and recent smoking were associated with cessation failure in 374 smokers (189, 50.5% female). Subjects were prompted to complete 4-7 real-time reports of craving, negative affect, and recent smoking daily in the four days prior to quitting. Multilevel models of craving and negative affect (mean level, growth, volatility, and association with smoking) were estimated. Results indicated that recent smoking was associated with significantly lower craving among smokers who failed to quit than those who achieved a full day of cessation, but this held only among smokers who reduced smoking by at least 10% in the days preceding the quit attempt. Smokers who failed to quit on the quit day also experienced slower increases in negative affect in the days preceding the quit attempt than did initial abstainers, but delayed quitters and delayed cessation failures did not differ in negative-affect trajectories. These results suggest that successful abstainers and cessation failures can be differentiated by specific dimensions of prequit craving and negative-affect experiences, but the effects hold only in certain circumstances. Yeh VM, McCarthy DE, Baker TB. An ecological momentary assessment analysis of prequit markers for smoking-cessation failure. Exp Clin Psychopharmacol. 2012 Dec; 20(6): 479-488. doi: 10.1037/a0029725. 2012 Aug 27. [Epub ahead of print].

A Randomized Trial of Intensive Outpatient (IOP) vs. Standard Outpatient (OP) Buprenorphine Treatment for African Americans Buprenorphine is increasingly being used in community-based treatment programs, but little is known about the optimal level of psychosocial counseling in these settings. The aim of this study was to compare the effectiveness of OP and IOP level counseling when provided as part of buprenorphine treatment for opioid-dependent African Americans. Participants were African American men and women starting buprenorphine treatment at one of two community-based clinics (N=300). Participants were randomly assigned to OP or IOP. Measures at baseline, 3- and 6-month included the primary outcome of DSM-IV opioid and cocaine dependence criteria, as well as additional outcomes of illicit opioid and cocaine use (urine test and self-report), criminal activity, retention in treatment, Quality of Life, Addiction Severity Index composite scores, and HIV risk behaviors. Participants assigned to OP received, on average, 3.67 (SD=1.30)h of counseling per active week in treatment. IOP participants received an average of 5.23 (SD=1.68)h of counseling per active week (less than the anticipated 9h per week of counseling). Both groups showed substantial improvement over a 6-month period on nearly all measures considered. There were no significant differences between groups in meeting diagnostic

criteria for opioid (p=.67) or cocaine dependence (p=.63). There were no significant between group differences on any of the other outcomes. A secondary analysis restricting the sample to participants meeting DSM-IV criteria for baseline cocaine dependence also revealed no significant between-group differences (all ps>.05). Buprenorphine patients receiving OP and IOP levels of care both show short-term improvements. Mitchell SG, Gryczynski J, Schwartz RP, O'Grady KE, Olsen YK, Jaffe JH. A randomized trial of intensive outpatient (IOP) vs. standard outpatient (OP) buprenorphine treatment for African Americans. Drug Alcohol Depend. 2013 Mar 1; 128(3): 222-229. doi: 10.1016/j.drugalcdep.2012.08.027. 2012 Sep 20. [Epub ahead of print].

RESEARCH ON PHARMACOTHERAPIES FOR DRUG ABUSE

Spontaneous Development of IgM Anti-Cocaine Antibodies in Habitual Cocaine Users: Effect on IgG Antibody Responses to a Cocaine Cholera Toxin B Conjugate Vaccine In cocaine vaccine studies, only a minority of subjects made strong antibody responses. To investigate this issue, IgG and IgM antibody responses to cocaine and to cholera toxin B (CTB-the carrier protein used to enhance immune responses to cocaine) were measured in sera from the 55 actively vaccinated subjects in a Phase IIb randomized double-blind placebo-controlled trial (TA-CD 109). Isotype specific ELISAs were used to measure IgG and IgM anti-cocaine and anti-CTB antibody in serial samples collected prior to and at intervals after immunization. The authors assessed IgG anti-cocaine responses of patients with pre-vaccination IgM anti-cocaine antibodies. Competitive inhibition ELISA was used to evaluate antibody specificity. Before immunization, 36/55 subjects had detectable IgM antibodies to cocaine, and 9 had IgM levels above the 95% confidence limit of 11μg/ml. These nine had significantly reduced peak IgG anti-cocaine responses at 16 weeks, and all were below the concentration (40μg/ml) considered necessary to discourage recreational cocaine use. The IgG anti-CTB responses of these same subjects were also reduced. Subjects who develop an IgM antibody response to cocaine in the course of repeated recreational exposure to this drug are significantly less likely to produce high levels of IgG antibodies from the cocaine conjugate vaccine. The failure may be due to recreational cocaine exposure induction of a type 2 T-cell independent immune response. Such individuals will require improved vaccines and are poor candidates for the currently available vaccine. Orson FM, Rossen RD, Shen X, Lopez AY, Wu Y, Kosten TR. Spontaneous development of Igm anti-cocaine antibodies in habitual cocaine users: Effect on Igg antibody responses to a cocaine cholera toxin b conjugate vaccine
Am J Addict. 2013 Mar; 22(2): 169-174.

Reduced Antinociception of Opioids in Rats and Mice by Vaccination with Immunogens Containing Oxycodone and Hydrocodone Haptens Prescription opioids abuse and associated deaths are an emerging concern in the USA. Vaccination against prescription opioids may provide an alternative to pharmacotherapy. An oxycodone hapten containing a tetraglycine linker at the C6 position (6OXY(Gly)(4)OH) conjugated to keyhole limpet hemocyanin (KLH) has shown early proof-of-efficacy in rodents as a candidate immunogen (6OXY(Gly)(4)-KLH) for the treatment of oxycodone abuse. In this study, oxycodone-based and hydrocodone-based haptens were conjugated to KLH to generate immunogens that would recognize both oxycodone and hydrocodone. Vaccination with 6OXY(Gly)(4)-KLH increased drug binding in serum, reduced drug distribution to brain, and blunted analgesia for both oxycodone and hydrocodone. An analogous C6-linked hydrocodone vaccine blocked hydrocodone effects but less so than 6OXY(Gly)(4)-KLH. C8-Linked hydrocodone immunogens had only limited efficacy. Amide conjugation showed higher haptenation ratios and greater efficacy than thioether conjugation to maleimide activated KLH (mKLH). The 6OXY(Gly)(4)-KLH vaccine may be used for treatment of prescription opioid abuse. Pravetoni M, Le Naour M, Tucker AM, Harmon TM, Hawley TM, Portoghese PS, Pentel PR. Reduced antinociception of opioids in rats and mice by vaccination with immunogens containing oxycodone and hydrocodone haptens . J Med Chem. 2013 Feb 14; 56(3): 915-923.

Selective Effects of a Morphine Conjugate Vaccine on Heroin and Metabolite Distribution and Heroin-Induced Behaviors in Rats Morphine conjugate vaccines have effectively reduced behavioral effects of heroin in rodents and primates. To better understand how these effects are mediated, heroin and metabolite distribution studies were performed in rats in the presence and absence of vaccination. In non-vaccinated rats 6-monoacetylmorphine (6-MAM) was the

predominant opioid in plasma and brain as early as 1 minute after i.v. administration of heroin and for up to 14 minutes. Vaccination with morphine conjugated to keyhole limpet hemocyanin (M-KLH) elicited high titers and concentrations of antibodies with high affinity for heroin, 6-MAM, and morphine. Four minutes after heroin administration vaccinated rats showed substantial retention of all three opioids in plasma compared to controls and reduced 6-MAM and morphine, but not heroin, distribution to brain. Administration of 6-MAM rather than heroin in M-KLH vaccinated rats showed a similar drug distribution pattern. Vaccination reduced heroin-induced analgesia and blocked heroin-induced locomotor activity throughout 2 weeks of repeated testing. Higher serum opioid-specific antibody concentrations were associated with higher plasma opioid concentrations, lower brain 6-MAM and morphine concentrations, and lower heroin-induced locomotor activity. Serum antibody concentrations over 0.2 mg/ml were associated with substantial effects on these measures. These data support a critical role for 6-MAM in mediating the early effects of i.v. heroin and suggest that reducing 6-MAM concentration in brain is essential to the efficacy of morphine conjugate vaccines. Raleigh MD, Pravetoni M, Harris AC, Birnbaum AK, Pentel PR. Selective effects of a morphine conjugate vaccine on heroin and metabolite distribution and heroin-induced behaviors in rats. J Pharmacol Exp Ther. 2013 Feb; 344(2): 397-406.

Modulating Cocaine Vaccine Potency Through Hapten Fluorination Cocaine addiction is a long-lasting relapsing illness characterized by cycles of abuse, abstinence, and reinstatement, and antibody-based therapies could be a powerful therapeutic approach. Herein, the authors explored the possibility of using halogenated cocaine haptens to enhance the immunological properties of anti-cocaine vaccines. Three fluorine-containing cocaine haptens (GNF, GNCF and GN5F) and one chlorine-containing cocaine hapten (GNCl) were designed and synthesized, based upon the chemical scaffold of the only hapten that has reached clinical trials, succinyl norcocaine (SNC). Hapten GNF was found to retain potent cocaine affinity, and also elicit antibodies in a higher concentration than the parent structure SNC. These data suggests that not only could strategic hapten fluorination be useful for improving upon the current cocaine vaccine undergoing clinical trials, but it may also be a valuable new approach, with application to any of the vaccines being developed for the treatment of drugs of abuse. Cai X, Tsuchikama K, Janda KD. Modulating cocaine vaccine potency through hapten fluorination. J Am Chem Soc. 2013 Feb 27; 135(8): 2971-2974.

Disrupted Adenovirus-Based Vaccines Against Small Addictive Molecules Circumvent Anti-Adenovirus Immunity Adenovirus (Ad) vaccine vectors have been used for many applications due to the capacity of the Ad capsid proteins to evoke potent immune responses, but these vectors are often ineffective in the context of pre-existing anti-Ad immunity. Leveraging the knowledge that E1(-)E3(-) Ad gene transfer vectors are potent immunogens, the authors have developed a vaccine platform against small molecules by covalently coupling analogs of small molecules to the capsid proteins of disrupted Ad (dAd5). They hypothesized that the dAd5 platform would maintain immunopotency even in the context of anti-Ad neutralizing antibodies. To test this hypothesis, they coupled cocaine and nicotine analogs, GNE and AM1, to dAd5 capsid proteins to generate dAd5GNE and dAd5AM1, respectively. Mice were pre-immunized with Ad5Null, resulting in high titer anti-Ad5 neutralizing antibodies comparable to those observed in the human population. The dAd5GNE and dAd5AM1 vaccines elicited high anti-cocaine and anti-nicotine antibody titers, respectively, in both naive and Ad5-immune mice, and both functioned to prevent cocaine or nicotine from reaching the brain of anti-Ad immune mice. Thus, disrupted Ad5 evokes potent humoral immunity that is effective in the context of pre-existing neutralizing anti-Ad immunity, overcoming a major limitation for current Ad-based vaccines. De BP, Pagovich OE, Hicks MJ,

Rosenberg JB, Moreno AY, Janda KD, Koob GF, Worgall S, Kaminsky SM, Sondhi D. Disrupted adenovirus-based vaccines against small addictive molecules circumvent anti-adenovirus immunity. Crystal RG Hum Gene Ther. 2013 Jan; 24(1): 58-66.

Individual Differences in Discount Rate are Associated with Demand for Self-Administered Cocaine, but not Sucrose Substance abusers, including cocaine abusers, discount delayed rewards to a greater extent than do matched controls. In the current experiment, individual differences in discounting of delayed rewards in rats (choice of one immediate over three delayed sucrose pellets) were assessed for associations with demand for either sucrose pellets or an intravenous dose of 0.1 mg/kg/infusion cocaine. Twenty-four male Sprague Dawley rats were split into three groups based on sensitivity to delay to reinforcement. Then, demand for sucrose pellets and cocaine was determined across a range of fixed-ratio values. Delay discounting was then reassessed to determine the stability of this measure over the course of the experiment. Individual differences in impulsive choice were positively associated with elasticity of demand for cocaine, a measure of reinforcer value, indicating that rats having higher discount rates also valued cocaine more. Impulsive choice was not associated with the level of cocaine consumption as price approached 0 or with any parameter associated with demand for sucrose. Individual sensitivity to delay was correlated with the initial assessment when reassessed at the end of the experiment, although impulsive choice increased for this cohort of rats as a whole. These findings suggest that impulsive choice in rats is positively associated with valuation of cocaine, but not sucrose. Koffarnus MN, Woods JH. Individual differences in discount rate are associated with demand for self-administered cocaine, but not sucrose. Addict Biol. 2013 Jan; 18(1): 8-18.

Diuretic Effects of Cannabinoids In vivo effects of cannabinoid (CB) agonists are often assessed using four well-established measures: locomotor activity, hypothermia, cataleptic-like effects, and analgesia. The present studies demonstrate that doses of CB agonists that produce these effects also reliably increase diuresis. Diuretic effects of several CB agonists were measured in female rats over 2 hours immediately after drug injection, and results were compared with hypothermic effects. Direct-acting CB1 agonists, including Δ(9)-tetrahydrocannabinol, WIN 55,212 [R-(1)-[2,3-dihydro-5-methyl-3-[(morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazinyl]-(1-naphthalenyl)methanone mesylate], AM2389 [9β-hydroxy-3-(1-hexyl-cyclobut-1-yl)-hexahydrocannabinol], and AM4054 [9β-(hydroxymethyl)-3-(1-adamantyl)-hexahydrocannabinol], produced dose-dependent increases in diuresis and decreases in colonic temperature, with slightly lower ED(50) values for diuresis than for hypothermia. The highest doses of cannabinoid drugs yielded, on average, 26-32 g/kg urine; comparable effects were obtained with 10 mg/kg furosemide and 3.0 mg/kg trans-(-)-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide (U50-488). Methanandamide (10.0 mg/kg) had lesser effect than other CB agonists, and the CB2 agonist AM1241 [1-(methylpiperidin-2-ylmethyl)-3-(2-iodo-5-nitrobenzoyl)indole], the anandamide transport inhibitor AM404, and the CB antagonist rimonabant did not have diuretic effects. In further studies, the diuretic effects of the CB1 agonist AM4054 were similar in male and female rats, displayed a relatively rapid onset to action, and were dose-dependently antagonized by 30 minutes pretreatment with rimonabant, but not by the vanilloid receptor type I antagonist capsazepine, nor were the effects of WIN 55,212 antagonized by the CB2 antagonist AM630 [(6-iodo-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl](4-methoxyphenyl) methanone)]. These data indicate that cannabinoids have robust diuretic effects in rats that are mediated via CB1 receptor mechanisms. Paronis CA, Thakur GA, Bajaj S, Nikas SP, Vemuri VK, Makriyannis A, Bergman J. Diuretic effects of cannabinoids. J Pharmacol Exp Ther. 2013 Jan; 344(1): 8-14.

The Antinociceptive Effects of Nicotinic Receptors A7-Positive Allosteric Modulators in Murine Acute and Tonic Pain Models The α7 nicotinic acetylcholine receptor (nAChR) subtype is abundantly expressed in the central nervous system and in the periphery. Recent evidence suggests that α7 nAChR subtypes, which can be activated by an endogenous cholinergic tone, comprising acetylcholine and the α7 nAChR agonist choline, play an important role in subchronic pain and inflammation. This study's objective was to test whether α7 nAChR positive allosteric modulators (PAMs) produce antinociception in in vivo mouse models of acute and persistent pain. Testing type I [N-(5-chloro-2-hydroxyphenyl)-N'-[2-chloro-5-(trifluoromethyl)phenyl] (NS1738)] and type II [1-(5-chloro-2,4-dimethoxy-phenyl)-3-(5-methyl-isoxazol-3-yl) (PNU-120596)] α7 nAChR PAMs in acute and persistent pain, the authors found that, although neither reduced acute thermal pain, only PNU-120596 dose-dependently attenuated paw-licking behavior in the formalin test. The long-acting effect of PNU-120596 in this test was in discordance with its pharmacokinetic profile in mice, which suggests the involvement of postreceptor signaling mechanisms. These results with selective mitogen-activated protein kinase inhibitor 1,4-diamino-2,3-dicyano-1,4-bis(o-aminophenylmercapto)butadiene monoethanolate (U0126) argues for an important role of extracellular signal-regulated kinase-1/2 pathways activation in PNU-120596's antinociceptive effects. The α7 antagonist MLA, administered intrathecally, reversed PNU-120596's effects, confirming PNU-120596's action, in part, through central α7 nAChRs. Importantly, tolerance to PNU-120596 was not developed after subchronic treatment of the drug. Surprisingly, PNU-120596's antinociceptive effects were blocked by NS1738. These results indicate that type II α7 nAChR PAM PNU-120596, but not type I α7 nAChR PAM NS1738, shows significant antinociception effects in persistent pain models in mice. Freitas K, Carroll FI, Damaj MI. The antinociceptive effects of nicotinic receptors A7-positive allosteric modulators in murine acute and tonic pain models. J Pharmacol Exp Ther. 2013 Jan; 344(1): 264-275.

Analysis of Tolerance and Behavioral/Physical Dependence during Chronic CB1 Agonist Treatment: Effects of CB1 Agonists, Antagonists, and Noncannabinoid Drugs Behavioral studies of chronic CB(1) receptor activation may provide a pharmacological approach to understanding efficacy-related differences among CB(1) ligands as well as mechanistic commonalities between cannabinoid and noncannabinoid drugs. In the present studies, the effects of CB(1) agonists [(6aR,10aR)-3-(1-adamantyl)-6,6,9-trimethyl-6a,7,10,10a-tetrahydrobenzo[c] chromen-1-ol (AM411), 9β-(hydroxymethyl)-3-(1-adamantyl)-hexahydrocannabinol (AM4054), R-(+)-[2,3-dihydro-5-methyl-3-[(morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazinyl]-(1-naphthalenyl)methanone mesylate (WIN55,212.2), Δ(9)-tetrahydrocannabinol (Δ(9)-THC), (R)-(+)-arachidonyl-1'-hydroxy-2'-propylamide (methanandamide)], CB(1) antagonists [5-(4-chlorophenyl)-1-(2,4-dichloro-phenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide (SR141716A), 5-(4-alkylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide (AM4113)], and dopamine (DA)-related [methamphetamine, (±)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide (SKF82958), (R)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SCH23390), (6aR)-5,6,6a,7-tetrahydro-6-propyl-4H-dibenzo[de,g]quinoline-10,11-diol (R-(-)-NPA), haloperidol] and opioid (morphine, naltrexone) drugs on scheduled-controlled responding under a 30-response fixed ratio schedule of stimulus-shock termination in squirrel monkeys were compared before and during chronic treatment with the long-acting CB(1) agonist AM411 (1.0 mg/kg per day, i.m.). Prechronic treatment with all drugs except naltrexone (1-10 mg/kg) produced dose-related decreases in responses rates. Dose-response re-determinations during chronic treatment revealed the following: 1) >250-fold (AM411, methanandamide) and >45-fold (AM4054, WIN55,212.2, Δ(9)-THC) rightward shifts in the ED(50) values for CB(1) agonists; 2) >100-fold and >20-fold leftward

shifts in the ED(50) values for SR141716A and AM4113, respectively; and 3) approximately 4.8-fold and 10-fold rightward shifts in the ED(50) values for methamphetamine and the DA D(2) agonist R-(-)-NPA, respectively. Dose-response relationships for other DA-related and opioid drugs were unchanged by chronic CB(1) agonist treatment. Differences in the magnitude of tolerance among CB(1) agonists during chronic treatment may be indicative of differences in their pharmacological efficacy, whereas the enhanced sensitivity to behaviorally disruptive effects of CB(1) antagonists may provide evidence for CB(1)-related behavioral and/or physical dependence. Finally, the development of cross-tolerance to methamphetamine and R-(-)-NPA bolsters previous evidence of interplay between CB(1) and DA D(2) signaling mechanisms. Desai RI, Thakur GA, Vemuri VK, Bajaj S, Makriyannis A, Bergman J. Analysis of tolerance and behavioral/physical dependence during chronic cb1 agonist treatment: effects of cb1 agonists, antagonists, and noncannabinoid drugs. J Pharmacol Exp Ther. 2013 Feb; 344(2): 319-328.

Variable Maternal Stress in Rats Alters Locomotor Activity, Social Behavior, and Recognition Memory in the Adult Offspring Rats repeatedly exposed to variable prenatal stress (PNS) exhibit behavioral signs that are similar to those manifested in several neuropsychiatric disorders such as deficits in attention and inhibitory control, and impairments in memory-related task performance. The purpose of the study described here was to conduct a comprehensive battery of tests to further characterize the behavioral phenotype of PNS rats as well as to evaluate the sensitivity of the model to therapeutic interventions (i.e., to compounds previously shown to have therapeutic potential in neuropsychiatric disorders). The results of this study indicated that PNS in rats is associated with: 1) increased locomotor activity and stereotypic behaviors, 2) elevated sensitivity to the psychostimulant amphetamine, 3) increased aggressive behaviors toward both adult and juvenile rats and 4) delay-dependent deficits in recognition memory. There was no evidence that PNS rats exhibited deficits in other areas of motor function/learning, sensorimotor gating, spatial learning and memory, social withdrawal, or anhedonia. In addition, the results revealed that the second generation antipsychotic risperidone attenuated amphetamine-related increases in locomotor activity in PNS rats; however, the effect was not sustained over time. Furthermore, deficits in recognition memory in PNS rats were attenuated by the norepinephrine reuptake inhibitor, atomoxetine, but not by the α7 nicotinic acetylcholine receptor partial agonist, GTS-21. This study supports the supposition that important phenomenological similarities exist between rats exposed to PNS and patients afflicted with neuropsychiatric disorders thus further establishing the face validity of the model for evaluating potential therapeutic interventions. Wilson CA, Terry AV Jr. Variable maternal stress in rats alters locomotor activity, social behavior, and recognition memory in the adult offspring. Pharmacol Biochem Behav. 2013 Mar; 104: 47-61. doi: 10.1016/j.pbb.2012.12.015. Epub 2012 Dec 31.

Exposure to Variable Prenatal Stress in Rats: Effects on Anxiety-Related Behaviors, Innate and Contextual Fear, and Fear Extinction Rats repeatedly exposed to variable prenatal stress (PNS) exhibit behavioral features often observed in neuropsychiatric disorders including elevated sensitivity to stimulants and impairments of attention, inhibitory control and memory-related task performance. However, to date there have been relatively few studies designed to assess the effects of PNS on anxiety, stress and fear responses, or the function of the hypothalamic-pituitary-adrenal (HPA) axis (a system clearly linked to stress and fear-related responses as well as neuropsychiatric disorders). In the current study, rats exposed to variable PNS were evaluated for anxiety-related behaviors in open field, elevated plus maze, and light/dark preference tasks. Innate fear responses were assessed using a predatory odor task and learned fear and extinction were assessed with a contextual fear conditioning task. As an indicator of HPA axis function, serum corticosterone levels

were determined by enzyme immunoassay at various time points. The results indicated that PNS resulted in several behavioral anomalies including decreased innate fear responses to predator odor, impaired fear extinction, increased locomotor activity and stereotypic-like behaviors. Baseline levels of corticosterone in PNS subjects were similar to non-stressed controls; however, when exposed to acute stress, they exhibited an increase in corticosterone that was greater in magnitude. PNS was not associated with increased anxiety-like behaviors or deficits in learning or retention during contextual fear conditioning. Collectivity, these data support the argument that variable PNS in rats is a valid model system for studying some behavioral components of neuropsychiatric disorders as well as the influence of stress hormones. Wilson CA, Vazdarjanova A, Terry AV Jr. Exposure to variable prenatal stress in rats: effects on anxiety-related behaviors, innate and contextual fear, and fear extinction**.** Behav Brain Res. 2013 Feb 1; 238: 279-288. doi: 10.1016/j.bbr.2012.10.003. Epub 2012 Oct 13.

Treatment of Cocaine Withdrawal Anxiety with Guanfacine: Relationships to Cocaine Intake and Reinstatement of Cocaine Seeking in Rats Successful treatment of cocaine addiction is severely impeded by the propensity of users to relapse. Withdrawal severity may serve as a key predictor of susceptibility to relapse. Therefore, the identification and treatment of cocaine withdrawal symptoms such as anxiety may improve addiction treatment outcome. The current study examined the role of anxiety-like behavior during cocaine withdrawal and anxiolytic treatment in reinstatement of cocaine seeking in an animal model of relapse. Male rats experienced daily IV cocaine self-administration. One group of animals received the norepinephrine α-2 agonist, guanfacine, or vehicle prior to anxiety testing 48 h after the last self-administration session. In the second group of rats, relationships between cocaine intake, anxiety-like behavior after withdrawal of cocaine, and reinstatement responding were investigated. The third and fourth groups of animals received guanfacine, yohimbine (norepinephrine α-2 antagonist), or vehicle once per day for 3 days 48 h after cessation of cocaine self-administration, followed by extinction and subsequent reinstatement induced by cocaine injections, cocaine-paired cues, and yohimbine administration. Cocaine-withdrawn rats at 48 h demonstrated higher levels of anxiety-like behavior as measured on a defensive burying task when compared to yoked saline controls, an effect reversed by guanfacine treatment. Cocaine intake was positively correlated with measures of anxiety-like behavior during early withdrawal, and this anxiety-like behavior was significantly correlated with subsequent cocaine-primed reinstatement. Yohimbine treatment during early withdrawal increased reinstatement to conditioned cues, while guanfacine treatment reduced reinstatement to yohimbine. These studies suggest an important role for noradrenergic mediation of anxiety-like behavior that emerges after withdrawal of cocaine and potential risk of relapse as modeled by reinstatement, and suggest that treatment of anxiety symptoms during early abstinence may reduce the risk of relapse. Buffalari DM, Baldwin CK, See RE. Treatment of cocaine withdrawal anxiety with guanfacine: relationships to cocaine intake and reinstatement of cocaine seeking in rats. Psychopharmacology (Berl). 2012 Sep;223(2):179-90. doi: 10.1007/s00213-012-2705-1. Epub 2012 Apr 18.

Effects of Chronic Buspirone Treatment on Nicotine and Concurrent Nicotine+Cocaine Self-Administration Nicotine dependence and cocaine abuse are major public health problems, and most cocaine abusers also smoke cigarettes. An ideal pharmacotherapy would reduce both cigarette smoking and cocaine abuse. Buspirone (Buspar) is a clinically available, non-benzodiazepine anxiolytic medication that acts on serotonin and dopamine systems. In preclinical studies, it reduced cocaine self-administration following both acute and chronic treatment in rhesus monkeys. The present study evaluated the effectiveness of chronic buspirone treatment on self-administration of intravenous (IV) nicotine and IV nicotine+cocaine combinations. Five cocaine-experienced adult

rhesus monkeys (Macaca mulatta) were trained to self-administer nicotine or nicotine+cocaine combinations, and food pellets (1g) during four 1-h daily sessions under a second-order schedule of reinforcement (FR 2 (VR16:S)). Each nicotine+cocaine combination maintained significantly higher levels of drug self-administration than nicotine or cocaine alone ($P<0.05$-0.001). Buspirone (0.032-0.56mg/kg/h) was administered IV through one lumen of a double-lumen catheter every 20min for 23h each day, for 7-10 consecutive days. Each 7-10-day sequence of buspirone treatment was followed by saline-control treatment for at least 3 days until food- and drug-maintained responding returned to baseline. Buspirone dose-dependently reduced responding maintained by nicotine alone (0.001-0.1mg/kg/inj; $P<0.01$) and by nicotine (0.001 or 0.0032mg/kg/inj)+cocaine combinations (0.0032mg/kg/inj; $P<0.05$-0.001) with no significant effects on food-maintained responding. The authors conclude that buspirone selectively attenuates the reinforcing effects of nicotine alone and nicotine+cocaine polydrug combinations in a nonhuman primate model of drug self-administration. Mello NK, Fivel PA, Kohut SJ. Effects of chronic buspirone treatment on nicotine and concurrent nicotine+cocaine self-administration. Neuropsychopharmacology. 2013 Jan 21. doi: 10.1038/npp.2013.25. [Epub ahead of print].

Preclinical Determinants of Drug Choice under Concurrent Schedules of Drug Self-Administration Drug self-administration procedures have played a critical role in the experimental analysis of psychoactive compounds, such as cocaine, for over 50 years. While there are numerous permutations of this procedure, this paper will specifically focus on choice procedures using concurrent schedules of intravenous drug self-administration. The aims of this paper are to first highlight the evolution of drug choice procedures and then review the subsequent preclinical body of literature utilizing these choice procedures to understand the environmental, pharmacological, and biological determinants of the reinforcing stimulus effects of drugs. A main rationale for this paper is our proposition that choice schedules are underutilized in investigating the reinforcing effects of drugs in assays of drug self-administration. Moreover, the authors will conclude with potential future directions and unexplored scientific space for the use of drug choice procedures. Banks ML and Negus SS. Preclinical determinants of drug choice under concurrent schedules of drug self-administration. Adv Pharmacol Sci. 2012; 2012: 281768. Published online 2012 November 28. doi: 10.1155/2012/281768

Role of Phenmetrazine as an Active Metabolite of Phendimetrazine: Evidence From Studies of Drug Discrimination and Pharmacokinetics in Rhesus Monkeys Monoamine releasers such as d-amphetamine that selectively promote release of dopamine/norepinephrine versus serotonin are one class of candidate medications for treating cocaine dependence; however, their clinical utility is limited by undesirable effects such as abuse liability. Clinical utility of these compounds may be increased by development of prodrugs to reduce abuse potential by slowing onset of drug effects. This study examined the behavioral and pharmacokinetic profile of the Schedule III compound phendimetrazine, which may serve as a prodrug for the N-demethylated metabolite and potent dopamine/norepinephrine releaser phenmetrazine. Monkeys (n=5) were trained in a two-key food-reinforced discrimination procedure to discriminate cocaine (0.32mg/kg, IM) from saline, and the potency and time course of cocaine-like discriminative stimulus effects were determined for (+)-phenmetrazine, (-)-phenmetrazine, (+)-phendimetrazine, (-)-phendimetrazine, and (±)-phendimetrazine. Parallel pharmacokinetic studies in the same monkeys examined plasma phenmetrazine and phendimetrazine levels for correlation with cocaine-like discriminative stimulus effects. Both isomers of phenmetrazine, and the racemate and both isomers of phendimetrazine, produced dose- and time-dependent substitution for the discriminative stimulus effects of cocaine, with greater potency residing in the (+) isomers. In general, plasma phenmetrazine levels increased

to similar levels after administration of behaviorally active doses of either phenmetrazine or phendimetrazine. These results support the hypothesis that phenmetrazine is an active metabolite that contributes to the effects of phendimetrazine. However, behavioral effects of phendimetrazine had a more rapid onset than would have been predicted by phenmetrazine levels alone, suggesting that other mechanisms may also contribute. Banks ML, Blough BE, Fennell TR, Snyder RW, Negus SS. Role of phenmetrazine as an active metabolite of phendimetrazine: Evidence from studies of drug discrimination and pharmacokinetics in rhesus monkeys. Drug Alcohol Depend. 2012 Dec 1. pii: S0376-8716(12)00426-7. doi: 10.1016/j.drugalcdep.2012.10.026. [Epub ahead of print],

Effects of Dopamine D2/D3 Receptor Ligands on Food-Cocaine Choice in Socially Housed Male Cynomolgus Monkeys Dopamine D2/D3 receptor partial agonists have been suggested as medications for cocaine dependence. The present experiments examined the effect of acute and repeated administration of drugs with varying intrinsic efficacy at D2/D3 receptors on the relative reinforcing strength of cocaine. Use of socially housed cynomolgus monkeys permitted the assessment of whether social status, known to alter D2/D3 receptor availability, influenced the behavioral effects of D2/D3 receptor compounds. The high-efficacy agonist R(-)-norpropylapomorphine [(-)-NPA], low-efficacy agonist aripiprazole (ARI), and antagonist eticlopride (ETIC) were administered acutely to monkeys self-administering cocaine under a food-cocaine choice procedure in which a cocaine self-administration dose-effect curve was determined daily. The effects of 5-day treatment with ARI and (-)-NPA were characterized under conditions in which monkeys did (ARI) or did not [ARI and (-)-NPA] self-administer cocaine during treatment. When administered acutely, ARI and ETIC increased the choice of low cocaine doses, and only (-)-NPA decreased the choice of higher cocaine doses and cocaine intake; effects were similar across social ranks. When administered repeatedly while self administration occurred only on days 1 and 5 of treatment, ARI, but not (-)-NPA, decreased cocaine choice in dominant monkeys, whereas (-)-NPA, but not ARI, did so in subordinates. When dominant monkeys self-administered cocaine on all five days of ARI treatment, however, these effects were not observed. The results indicate that the behavioral effects of D2/D3 receptor agonists can differ according to intrinsic efficacy and subject characteristics. Moreover, these results suggest that exposure to cocaine during treatment can counteract treatment-induced reductions in the reinforcing effects of cocaine. Czoty PW, Nader MA. Effects of dopamine D2/D3 receptor ligands on food-cocaine choice in socially housed male cynomolgus monkeys. J Pharmacol Exp Ther. 2013 Feb;34 4(2): 329-338. doi: 10.1124/jpet.112.201012. Epub 2012 Dec 4.

Positive Allosteric Modulation of Mglur5 Accelerates Extinction Learning but not Relearning Following Methamphetamine Self-Administration Recent studies have implicated glutamate neurotransmission as an important substrate for the extinction of conditioned behaviors, including responding for drug reinforcement. Positive allosteric modulation of the type-5 metabotropic glutamate receptor (mGluR5) in particular has emerged as a treatment strategy for the enhancement of extinction of drug-motivated behaviors. Here, the authors investigated the effects of the mGluR5 positive allosteric modulator CDPPB, a compound known for its cognitive enhancing effects in rodents, on extinction learning in rats with different histories of methamphetamine (METH) training. Rats were trained to self-administer METH under two conditions: 16 daily sessions of short access (90min/day, ShA), or eight daily sessions of short access followed by eight sessions of long access (6h/day, LgA). Control rats self-administered sucrose pellets in daily 30 min sessions. Next, rats were administered vehicle or 30mg/kg CDPPB prior to seven consecutive daily extinction sessions, subjected to additional extinction sessions to re-establish a post-treatment baseline, and

then tested for reinstatement of behavior in the presence of METH- or sucrose-paired cues. Rats were then subjected to a second series of extinction sessions, preceded by vehicle or 30mg/kg CDPPB, and an additional test for cue-triggered reinstatement. CDPPB treatment resulted in a more rapid extinction of responding on the active lever, especially in the early sessions of the first extinction sequence. However, treatment effects were minimal during subsequent cue reinstatement tests and non-existent during the second series of extinction sessions. Rats with histories of ShA, LgA, and sucrose training expressed similar behavioral sensitivities to CDPPB, with LgA rats demonstrating a modestly higher treatment effect. Positive allosteric modulation of mGluR5 may therefore have some beneficial effects on efforts to facilitate. Kufahl PR, Hood LE, Nemirovsky NE, Barabas P, Halstengard C, Villa A, Moore E, Watterson LR, Olive MF. Positive allosteric modulation of mGluR5 accelerates extinction learning but not relearning following methamphetamine self-administration. Front Pharmacol. 2012; 3: 194. doi: 10.3389/fphar.2012.00194. Epub 2012 Nov 26.

Attenuation of Reinstatement of Methamphetamine-, Sucrose-, and Food-Seeking Behavior in Rats by Fenobam, a Metabotropic Glutamate Receptor 5 Negative Allosteric Modulator
Methamphetamine (METH) is a highly potent and addictive psychostimulant with severe detrimental effects to the health of users. Currently, METH addiction is treated with a combination of cognitive and behavioral therapies, but these traditional approaches suffer from high relapse rates. Furthermore, there are currently no pharmacological treatment interventions approved by the FDA specifically for the treatment of METH addiction. Metabotropic glutamate receptor 5 (mGluR5) negative allosteric modulators (NAMs) have shown promise in significantly attenuating drug self-administration and drug-seeking in reinstatement paradigms. However, studies assessing the potential efficacy of mGluR5 NAMs that have been tested in human subjects are lacking. The current study sought to assess the effect of the mGluR5 NAM fenobam on METH-seeking behavior. Rats were trained to self-administer METH (0.05 mg/kg i.v.), and following extinction, tested for effects of fenobam (5, 10, or 15 mg/kg intraperitoneal) on cue- and drug-induced reinstatement of METH-seeking. To determine if fenobam also alters reinstatement of seeking of natural reinforcers, separate groups of rats were trained to self-administer sucrose or food pellets and were tested for the effects of fenobam on cue-induced reinstatement of sucrose- and food-seeking. Fenobam attenuated drug- and cue-induced reinstatement of METH-seeking behavior at doses of 10 and 15 mg/kg. Fenobam also attenuated cue-induced reinstatement of sucrose- and food-seeking at all doses tested. The mGluR5 NAM fenobam attenuates the reinstatement of METH-seeking behavior, but these effects may be due to nonspecific suppression of general appetitive behaviors. Watterson LR, Kufahl PR, Nemirovsky NE, Sewalia K, Hood LE, Olive MF. Attenuation of reinstatement of methamphetamine-, sucrose-, and food-seeking behavior in rats by fenobam, a metabotropic glutamate receptor 5 negative allosteric modulator. Psychopharmacology (Berl). 2013 Jan; 225(1): 151-159. doi: 10.1007/s00213-012-2804-z. Epub 2012 Jul 21.

The Alpha-1 Adrenergic Antagonist Doxazosin for Treatment of Cocaine Dependence: A Pilot Study Medications decreasing central noradrenergic activity have been associated with attenuation of cocaine effects. This pilot study examined the efficacy of doxazosin versus placebo for reducing cocaine use in treatment-seeking cocaine dependent persons.The authors screened 108 cocaine dependent subjects and assigned 35 participants to receive either doxazosin (8mg/day) or placebo for 13 weeks. Participants were titrated on the study medication according to two different schedules. During the initial phase of the study, patients were titrated onto the study medication over an 8-week period (DOX-slow). After reviewing data from the authors' human laboratory study, a second phase was initiated, wherein titration was accelerated to a 4-week period (DOX-

fast). All participants received weekly cognitive behavioral therapy. Urine toxicology was performed thrice weekly. Baseline subject characteristics were comparable. Thirty subjects entered the study: 8 subjects in DOX-slow, 9 subjects in DOX-fast, and 13 subjects in placebo. Total number of cocaine-negative urines was significantly increased in the DOX-fast group; and percentage of total cocaine-negative urines by group were 10% for DOX-slow group, 35% for DOX-fast group, and 14% for placebo ($\chi(2)=36.3$, df=2, $p<0.0001$). The percentage of participants achieving two or more consecutive weeks of abstinence by group was 0% for DOX-slow group, 44% for DOX-fast group, and 7% for placebo ($\chi(2)=7.35$, df=2, $p<0.023$). This pilot study suggests the potential efficacy of doxazosin when rapidly titrated in reducing cocaine use. Shorter D, Lindsay JA, Kosten TR. The alpha-1 adrenergic antagonist doxazosin for treatment of cocaine dependence: A pilot study. Drug Alcohol Depend. 2013 Jan 7 [Epub ahead of print].

DBH Gene as Predictor of Response in a Cocaine Vaccine Clinical Trial The authors examined a pharmacogenetic association of the dopamine β-hydroxylase (DBH) gene with a response to an anti-cocaine vaccine that was tested in a recent clinical trial. This gene is associated with cocaine-induced paranoia, which has a slower onset than the euphoria from cocaine. The vaccine reduced euphoria by slowing the entry of cocaine into the brain, but it may not reduce aversive symptoms like paranoia. A16-week Phase IIb randomized double-blind placebo-controlled trial of 114 cocaine and opioid dependent subjects who received five vaccinations over the first 12 weeks was examined. The authors genotyped 71 subjects for the rs1611115 (-1021C>T) variant of the DBH gene and compared vaccine to placebo subjects on cocaine-free urines. Using repeated measures analysis of variance, corrected for population structure, vaccine pharmacotherapy reduced cocaine positive urines significantly based on DBH genotype. Patients with the low DβH level genotype dropped from 77% to 51% on vaccine (p=0.0001), while those with the normal DβH level genotype dropped from 83% to 72%. Placebo showed no effect on cocaine use overall or by genotype. This study indicates that a patient's DBH genotype could be used to identify a subset of individuals for whom vaccine treatment may be an effective pharmacotherapy for cocaine dependence. Kosten TR, Domingo CB, Hamon SC, Nielsen DA. DBH gene as predictor of response in a cocaine vaccine clinical trial. Neurosci Lett. 2013 Feb 28 [Epub ahead of print].

Opioid-Like Effects of the Neurokinin 1 Antagonist Aprepitant in Patients Maintained on and Briefly Withdrawn from Methadone Although opioid substitution therapy is an effective clinical tool used to manage opioid abuse and dependence, concerns regarding the current FDA-approved medications have lead to a search for efficacious, non-opioid medications. Preclinical data indicate that neurokinin 1 (NK1) receptor activity may modulate opioid effects and withdrawal. This investigation sought to examine the ability of the NK1 antagonist aprepitant to alter the effects of methadone as well as withdrawal symptoms induced by brief methadone discontinuation. This blinded, placebo-controlled, within-subjects study consisted of placebo and aprepitant conditions. Experimental assessments occurred on the first three days (days 1-3: placebo or aprepitant + methadone) and again on days 8-10 (aprepitant or placebo + methadone). Fifteen methadone-maintained patients completed the investigation. Outcome measures were the assessments of opioid withdrawal, as well as subjective measures of opioid-like effects. Statistical trends indicated that aprepitant may reduce opioid withdrawal symptoms. When an active dose of aprepitant was administered an hour before methadone, participants reported less desire to use methadone. However, ratings of methadone "Liking" also appeared to increase. These data tentatively suggest that aprepitant has some ability to alleviate withdrawal following methadone abstinence, but also appears to increase subjective indicators of methadone's abuse liability. Since few of the differences between aprepitant and placebo reached statistical significance, these data should only be viewed as

preliminary. Findings from other studies indicate that higher doses of aprepitant may be more clinically effective. Further clinical investigations are needed in order to determine whether aprepitant is useful for alleviating opioid withdrawal. Jones JD, Speer T, Comer SD, Ross S, Rotrosen J, Reid MS. Opioid-like effects of the neurokinin 1 antagonist aprepitant in patients maintained on and briefly withdrawn from methadone. Am J Drug Alcohol Abuse 2013 Mar; (2): 86-91.

High Dose Transdermal Nicotine for Fast Metabolizers of Nicotine: A Proof of Concept Placebo-Controlled Trial Smokers with a faster rate of nicotine metabolism, estimated using the ratio of 3'-hydroxycotinine (3-HC) to cotinine, have lower plasma nicotine levels and are more likely to relapse with 21 mg nicotine patch therapy, than smokers with slower rates of nicotine metabolism. Thus, faster metabolizers of nicotine may require a higher nicotine patch dose to achieve cessation. This proof of concept randomized placebo-controlled trial evaluated the efficacy and safety of 8 weeks of 42 mg transdermal nicotine versus 21 mg, among 87 fast metabolizers of nicotine (3-HC/cotinine ≥ 0.18).After 1 week of treatment, an intent-to-treat (ITT) analysis showed that participants treated with 42 mg nicotine had significantly higher expired-air carbon monoxide (CO)-confirmed 24-hr abstinence (75% vs. 58.1%; OR = 3.21; 95% CI: 1.12-9.24, p = .03) but not 7-day abstinence (50% vs. 34.9%; OR = 2.02; 95% CI: 0.82-4.94, p = .13). After 8 weeks of treatment, ITT analysis showed that participants treated with 42 mg nicotine had marginally higher rates of CO-confirmed 24-hr abstinence (45.5% vs. 30.2%; OR = 2.32; 95% CI: 0.92-5.92, p = .08) but not 7-day abstinence (29.6% vs. 23.3%; OR = 1.52, 95% CI: 0.57-4.07, p = .41). Percent nicotine and cotinine replacement were significantly greater for 42 mg nicotine versus 21 mg (p < .005). There were no significant differences between treatment arms in the frequency of severe side effects and serious adverse events or blood pressure during treatment (p > .10).Further examination of the efficacy of 42 mg nicotine patch therapy for fast metabolizers of nicotine is warranted. Schnoll RA, Wileyto EP, Leone FT, Tyndale RF, Benowitz NL. High dose transdermal nicotine for fast metabolizers of nicotine: a proof of concept placebo-controlled trial. Nicotine Tob Res 2013 Feb; (2): 348-354.

Dependence and Withdrawal-Induced Craving Predict Abstinence in an Incentive-Based Model of Smoking Relapse Understanding factors that render some individuals more vulnerable to smoking relapse during the early stages of a quit attempt is critical to tailoring treatment efforts. Development of laboratory models of relapse can provide a framework for identifying underlying mechanisms that may contribute to vulnerability. Here, the authors explored predictors of abstinence in a novel incentive-based model of relapse.Fifty-six nontreatment seeking daily smokers completed several nicotine dependence measures prior to participating in a 1-week abstinence incentive test. During the abstinence procedure, participants earned monetary reinforcement for each biochemically verified day of abstinence according to a descending schedule of reinforcement. Compliance with the procedure was excellent. All but 3 participants were able to initiate abstinence; nearly 70% lapsed as incentives were reduced. Scores on the Fagerström Test for Nicotine Dependence (FTND), number of cigarettes smoked per day, and self-reported craving on the first day of abstinence each independently predicted time to lapse. The single item of time to first cigarette in the morning on the FTND significantly predicted time to lapse, even when controlling for other significant predictors just listed. The Nicotine Dependence Syndrome Scale (NDSS) and Wisconsin Inventory of Smoking Dependence Motives did not predict lapse, but the NDSS did predict reinitiation of abstinence among those experiencing an initial lapse. These findings partially replicate those of previous full-scale clinical trials and support the feasibility and validity of an incentive-based model of relapse. The time-limited and laboratory-based nature of

this model has the potential to further investigations of underlying mechanisms contributing to relapse. Sweitzer MM, Denlinger RL, Donny EC. Dependence and withdrawal-induced craving predict abstinence in an incentive-based model of smoking relapse. Nicotine Tob Res 2013 Jan; (1): 36-43.

Alternative Reinforcer Response Cost Impacts Methamphetamine Choice in Humans Methamphetamine use disorders are a persistent public health concern. Behavioral treatments have demonstrated that providing access to non-drug alternative reinforcers reduces methamphetamine use. The purpose of this human laboratory experiment was to determine how changes in response cost for non-drug alternative reinforcers influenced methamphetamine choice. Seven subjects with past year histories of recreational stimulant use completed a placebo-controlled crossover double-blind protocol in which they first sampled doses of oral methamphetamine (0 8 or 16 mg) and completed a battery of subject-rated and physiological measures. During subsequent sessions subjects then made eight discrete choices between 1/8th of the sampled dose and an alternative reinforcer ($0.25). The response cost to earn a methamphetamine dose was always 500 responses (FR500). The response cost for the alternative reinforcer varied across sessions (FR500 FR1000 FR2000 FR3000). Methamphetamine functioned as a positive reinforcer and produced prototypical stimulant-like effects (e.g. elevated blood pressure increased ratings of Stimulated). Choice for doses over money was sensitive to changes in response cost for alternative reinforcers in that more doses were taken at higher FR values than at lower FR values. Placebo choices changed as a function of alternative reinforcer response cost to a greater degree than active methamphetamine choices. These findings suggest that manipulating the effort necessary to earn alternative reinforcers could impact methamphetamine use. Bennett JA, Stoops WW, Rush CR. Alternative reinforcer response cost impacts methamphetamine choice in humans. Pharmacol Biochem Behav 2013 Jan, (3): 481-486.

A Randomized Double-Blind, Placebo Controlled Trial of Venlafaxine-Extended Release For Co-Occurring Cannabis Dependence and Depressive Disorders The aim of this study was to evaluate whether venlafaxine-extended release (VEN-XR) is an effective treatment for cannabis dependence with concurrent depressive disorders. This was a randomized, 12 week, double-blind, placebo-controlled trial of outpatients (n = 103) with DSM-IV cannabis dependence and major depressive disorder or dysthymia. Participants received up to 375 mg VEN-XR on a fixed-flexible schedule or placebo. All patients received weekly individual cognitive-behavioral psychotherapy that primarily targeted marijuana use. The trial was conducted at two university research centers in the United States. One hundred and three cannabis dependent adults participated in the trial. The primary outcome measures were 1) abstinence from marijuana defined as at least two consecutive urine-confirmed abstinent weeks and 2) improvement in depressive symptoms based on the Hamilton Depression Rating Scale. The proportion of patients achieving a clinically significant mood improvement [50% decrease in Hamilton Depression score from baseline] was high and did not differ between groups receiving VEN-XR (63%) and placebo (69%) (X(1) (2) =0.48, p-value= 0.49). The proportion of patients achieving abstinence was low overall, but was significantly worse on VEN-XR (11.8%) compared to placebo (36.5%) (X(1) (2) =7.46, p-value<0.01; OR = 4.51, 95% CI: 1.53, 13.3). Mood improvement was associated with reduction in marijuana use in the placebo group (F(1,179) =30.49, p-value<0.01), but not the VEN-XR group (F(1,186) =0.02, p-value=0.89). For depressed, cannabis-dependent patients, venlafaxine-extended release does not appear to be effective at reducing depression and may lead to an increase in cannabis use. Levin FR, Mariani J, Brooks DJ, Pavlicova M, Nunes EV, Agosti V, Bisaga A, Sullivan MA, Carpenter KM. A

randomized double-blind, placebo controlled trial of Venlafaxine-Extended release for co-occurring cannabis dependence and depressive disorders. Addiction. 2013 Jan 8. [Epub ahead of print].

Nabilone Decreases Marijuana Withdrawal and a Laboratory Measure of Marijuana Relapse

Few individuals seeking treatment for marijuana use achieve sustained abstinence. The cannabinoid receptor agonist, Δ(9)-tetrahydrocannabinol (THC; dronabinol), decreases marijuana withdrawal symptoms, yet does not decrease marijuana use in the laboratory or clinic. Dronabinol has poor bioavailability, which may contribute to its poor efficacy. The FDA-approved synthetic analogue of THC, nabilone, has higher bioavailability and clearer dose-linearity than dronabinol. This study tested whether nabilone administration would decrease marijuana withdrawal symptoms and a laboratory measure of marijuana relapse relative to placebo. Daily, nontreatment-seeking marijuana smokers (8M, 3F), who reported smoking 8.3±3.1 marijuana cigarettes/day completed this within-subject study comprising three, 8-day inpatient phases; each phase tested a different nabilone dose [0, 6, 8mg/day, administered in counter-balanced order on days 2-8]. On the first inpatient day, participants took placebo capsules and smoked active marijuana (5.6% THC) at six timepoints. For the next 3 days, they had the opportunity to self-administer placebo marijuana (0.0% THC; Withdrawal), followed by 4 days in which active marijuana was available for self-administration (5.6% THC; Relapse). Both nabilone dose conditions decreased marijuana relapse and reversed withdrawal-related irritability and disruptions in sleep and food intake ($p<0.05$). Nabilone (8mg/day) modestly worsened psychomotor task performance. Neither dose condition increased ratings of capsule 'liking'or desire to take the capsules relative to placebo. Thus, nabilone maintenance produced a robust attenuation of marijuana withdrawal symptoms and a laboratory measure of relapse even with once per day dosing. These data support testing of nabilone for patients seeking marijuana treatment. Haney M, Cooper ZD, Bedi G, Vosburg SK, Comer SD, Foltin RW. Nabilone decreases marijuana withdrawal and a laboratory measure of marijuana relapse. Neuropsychopharmacology. 2013 Feb 26 [Epub ahead of print].

RESEARCH ON THE MEDICAL CONSEQUENCES OF DRUG ABUSE AND CO-OCCURRING INFECTIONS

Medicinal and Recreational Marijuana Use Among HIV-infected Women in the Women's Interagency HIV Study (WIHS) Cohort, 1994-2010 Despite the major benefits of effective antiretroviral therapy on HIV-related survival, there is an ongoing need to help alleviate medication side effects related to antiretroviral therapy use. Initial studies suggest that marijuana use may reduce HIV-related symptoms, but medical marijuana use among HIV-infected individuals has not been well described. The authors evaluated trends in marijuana use and reported motivations for use among 2776 HIV-infected women in the Women's Interagency HIV Study between October 1994 and March 2010. Predictors of any and daily marijuana use were explored in multivariate logistic regression models clustered by person using generalized estimating equation. In 2009, participants were asked if their marijuana use was medical, "meaning prescribed by a doctor," or recreational, or both. Over the 16 years of this study, the prevalence of current marijuana use decreased significantly from 21% to 14%. In contrast, daily marijuana use almost doubled from 3.3% to 6.1% of all women and from 18% to 51% of current marijuana users. Relaxation, appetite improvement, reduction of HIV-related symptoms, and social use were reported as common reasons for marijuana use. In 2009, most marijuana users reported either purely medicinal use (26%) or both medicinal and recreational usage (29%). Daily marijuana use was associated with higher CD4 cell count, quality of life, and older age. Demographic characteristics and risk behaviors were associated with current marijuana use overall but were not predictors of daily use. This study suggests that both recreational and medicinal marijuana use are relatively common among HIV-infected women in the United States. D'souza G, Matson PA, Grady CD, Nahvi S, Merenstein D, Weber KM, Greenblatt R, Burian P, Wilson TE. Medicinal and recreational marijuana use among HIV-infected women in the Women's Interagency HIV Study (WIHS) cohort, 1994-2010. J Acquir Immune Defic Syndr. 2012 Dec 15; 61(5): 618-626.

HIV and Recent Illicit Drug Use Interact to Affect Verbal Memory in Women HIV infection and illicit drug use are each associated with diminished cognitive performance. This study examined the separate and interactive effects of HIV and recent illicit drug use on verbal memory, processing speed and executive function in the multicenter Women's Interagency HIV Study (WIHS). Participants included 952 HIV-infected and 443 HIV-uninfected women (mean age=42.8, 64% African-American). Outcome measures included the Hopkins Verbal Learning Test - Revised (HVLT-R) and the Stroop test. Three drug use groups were compared: recent illicit drug users (cocaine or heroin use in past 6 months, n=140), former users (lifetime cocaine or heroin use but not in past 6 months, n=651), and non-users (no lifetime use of cocaine or heroin, n=604). The typical pattern of recent drug use was daily or weekly smoking of crack cocaine. HIV infection and recent illicit drug use were each associated with worse verbal learning and memory (p's<.05). Importantly, there was an interaction between HIV serostatus and recent illicit drug use such that recent illicit drug use (compared to non-use) negatively impacted verbal learning and memory only in HIV-infected women (p's <0.01). There was no interaction between HIV serostatus and illicit drug use on processing speed or executive function on the Stroop test. The interaction between HIV serostatus and recent illicit drug use on verbal learning and memory suggests a potential synergistic neurotoxicity that may affect the neural circuitry underlying performance on these tasks. Grauzas V, Rubin LH, Martin E, Weber KM, Cohen MH, Golub ET, Valcour V, Young MA, Crystal H, Anastos K, Aouizerat BE, Milam J, Maki PM. HIV and recent illicit drug use interact to affect verbal memory in women. J Acquir Immune Defic Syndr. 2013 Feb 7. [Epub ahead of print].

Alcohol Consumption and CD4 T-Cell Count Response Among Persons Initiating Antiretroviral Therapy In this study the authors evaluated the longitudinal association of alcohol use with immunologic response to combination antiretroviral therapy (ART) among HIV-infected individuals. This was a prospective cohort study of individuals initiating ART. Participants underwent an Audio Computer-Assisted Self-interview querying drug and alcohol use within 6 months of treatment. Immunologic response to ART was defined by CD4 T-cell count (CD4). Primary independent variables were self-reported number of drinks consumed per drinking day (quantity) and days of alcohol consumption in a typical week (frequency). The authors used linear mixed effects models to quantify the association between CD4 T-cell count and alcohol quantity and frequency and Cox proportional hazards models to estimate the relative hazard of an increase in 100, 150, and 200 CD4 cells per cubic millimeter per additional drink per drinking day. Analyses were stratified by sex. Viral suppression was examined as a time-varying covariate. Between 2000 and 2008, 1107 individuals were eligible for inclusion in this study. There was no statistically significant difference in CD4 T-cell count by average drinks per drinking day at any frequency of alcohol use irrespective of sex or viral suppression. Similarly, the authors found no difference in the hazard ratio for drinks per drinking day within the categories of drinking frequency for time to CD4 T-cell count increase of 100, 150, and 200 cells per cubic millimeter, respectively. The authors conclude that among individuals initiating ART, the benefits of therapy and viral suppression on the immune system outweigh detrimental effects of alcohol, reinforcing the importance of initiating ART and ensuring adequate adherence to therapy. Kowalski S, Colantuoni E, Lau B, Keruly J, McCaul ME, Hutton HE, Moore RD, Chander G. Alcohol consumption and CD4 T-cell count response among persons initiating antiretroviral therapy. J Acquir Immune Defic Syndr. 2012 Dec 1; 61(4): 455-461.

Metropolitan Social Environments and Pre-HAART/HAART Era Changes in Mortality Rates (per 10,000 Adult Residents) among Injection Drug Users Living with AIDS Among the largest US metropolitan areas, trends in mortality rates for injection drug users (IDUs) with AIDS vary substantially. Ecosocial, risk environment and dialectical theories suggest many metropolitan areas characteristics that might drive this variation. The authors assess metropolitan area characteristics associated with decline in mortality rates among IDUs living with AIDS (per 10,000 adult MSA residents) after highly active antiretroviral therapy (HAART) was developed. This is an ecological cohort study of 86 large US metropolitan areas from 1993-2006. The proportional rate of decline in mortality among IDUs diagnosed with AIDS (as a proportion of adult residents) from 1993-1995 to 2004-2006 was the outcome of interest. This rate of decline was modeled as a function of MSA-level variables suggested by ecosocial, risk environment and dialectical theories. In multiple regression analyses, we used 1993-1995 mortality rates to (partially) control for pre-HAART epidemic history and study how other independent variables affected the outcomes. In multivariable models, pre-HAART to HAART era increases in 'hard drug' arrest rates and higher pre-HAART income inequality were associated with lower relative declines in mortality rates. Pre-HAART per capita health expenditure and drug abuse treatment rates, and pre- to HAART-era increases in HIV counseling and testing rates, were weakly associated with greater decline in AIDS mortality. The authors conclude that mortality among IDUs living with AIDS might be decreased by reducing metropolitan income inequality, increasing public health expenditures, and perhaps increasing drug abuse treatment and HIV testing services. Given prior evidence that drug-related arrest rates are associated with higher HIV prevalence rates among IDUs and do not seem to decrease IDU population prevalence, changes in laws and policing practices to reduce such arrests while still protecting public order should be considered. Friedman SR, West BS, Pouget ER, Hall HI, Cantrell J, Tempalski B, Chatterjee S, Hu X, Cooper HL, Galea S, Des Jarlais DC. Changes in mortality

rates (per 10,000 adult residents) among injection drug users living with AIDS. PLoS One. 2013; 8(2): e57201.

Current Management of Hepatitis C Virus Infection in Patients With HIV Co-Infection
As a result of shared routes of transmission, coinfection with hepatitis C virus (HCV) is common in human immunodeficiency virus (HIV)-infected patients. The prevalence of HIV/HCV coinfection is particularly high among persons who have used injection drugs; however, more recently, sexual transmission of HCV has been recognized among HIV-infected men who have sex with men (MSM). Over the past decade, the effectiveness of HIV treatment improved substantially, leading to a substantial reduction in HIV/AIDS-related deaths; in this context, liver disease due to HCV infection has emerged as major concern for co-infected patients. Over the same period, treatment of HCV remained stagnant, with pegylated interferon alfa (PegIFN) plus ribavirin (RBV; PegIFN/RBV) entrenched as the standard treatment for HCV infection for co-infected patients, who have the greatest risk for liver disease. However, the effectiveness of HCV treatment in this population has been disappointing because of low rates of treatment initiation and success. In 2011, novel HCV NS3/4A PIs (PIs), telaprevir and boceprevir, were approved for use in combination with PegIFN/RBV for the treatment of HCV genotype 1 infection; at the time of approval, important questions regarding the efficacy, safety, and potential for drug interactions with telaprevir and boceprevir had not been answered. More recently, data from drug-interaction studies and 2 small, phase II clinical trials indicate that these HCV treatment regimens may lead to higher rates of HCV eradication in HIV/HCV-coinfected patients, with manageable toxicity and pharmacologic interactions with antiretroviral drugs. As such, these HCV PI-based regimens have emerged as the standard for the treatment of HCV genotype 1 infection in carefully selected HIV-infected patients. Sulkowski MS. Current management of hepatitis C virus infection in patients with HIV co-infection. J Infect Dis. 2013 Mar; 207 Suppl 1: S26-32

Breaking Down the Barriers to Hepatitis C Virus (HCV) Treatment Among Individuals with HCV/HIV Coinfection: Action Required at the System, Provider, and Patient Levels The majority of hepatitis C virus (HCV) and human immunodeficiency virus (HIV) coinfection occurs among persons who inject drugs. Rapid improvements in responses to HCV therapy have been observed, but liver-related morbidity rates remain high, given notoriously low uptake of HCV treatment. Advances in HCV therapy will have a limited impact on the burden of HCV-related disease at the population-level unless barriers to HCV education, screening, evaluation, and treatment are addressed and treatment uptake increases. This review will outline barriers to HCV care in HCV/HIV coinfection, with a particular emphasis on persons who inject drugs, proposing strategies to enhance HCV treatment uptake and outcomes. Grebely J, Oser M, Taylor LE, Dore GJ. Breaking down the barriers to hepatitis C virus (HCV) treatment among individuals with HCV/HIV coinfection: action required at the system, provider, and patient levels. J Infect Dis. 2013 Mar; 207 Suppl 1: S19-25.

HIV Coinfection with Hepatitis C Virus: Evolving Epidemiology and Treatment Paradigms
Chronic hepatitis C virus (HCV) infection has become a major threat to the survival of human immunodeficiency virus (HIV)-infected persons in areas where antiretroviral therapy is available. In coinfection, viral eradication has been difficult to attain, and HCV therapy is underused. Novel therapies may be particularly beneficial for this population, yet studies lag behind those for HCV monoinfection. Increasingly, incident HCV among HIV-infected men who have sex with men is associated with sexual risk behavior further research should be performed to refine understanding of the causal mechanism of this association. The phenomenon of aggressive hepatic fibrogenesis when

HIV infection precedes HCV acquisition requires longer-term observation to ensure optimal timing of HCV therapy. Medical management in coinfection will be improved by enhancing HCV detection, with annual serologic testing, screening with HCV RNA to detect acute infection, and HIV testing of HCV-infected individuals; by addressing HCV earlier in coinfected persons; and by universal consideration for HCV therapy. HCV drug trials in individuals coinfected with HIV should be expedited. HIV/HCV coinfection remains a growing and evolving epidemic; new developments in therapeutics and improved care models offer promise. Taylor LE, Swan T, Mayer KH. HIV coinfection with hepatitis C virus: evolving epidemiology and treatment paradigms. Clin Infect Dis. 2012 Jul; 55 Suppl 1: S33-42.

Constraints on Viral Evolution During Chronic Hepatitis C Virus Infection Arising From a Common-Source Exposure Extraordinary viral sequence diversity and rapid viral genetic evolution are hallmarks of hepatitis C virus (HCV) infection. Viral sequence evolution has previously been shown to mediate escape from cytotoxic T-lymphocyte (CTL) and neutralizing antibody responses in acute HCV infection. HCV evolution continues during chronic infection, but the pressures driving these changes are poorly defined. The authors analyzed plasma virus sequence evolution in 5.2-kb hemigenomes from multiple longitudinal time points isolated from individuals in the Irish anti-D cohort, who were infected with HCV from a common source in 1977 to 1978. They found phylogenetically distinct quasispecies populations at different plasma time points isolated late in chronic infection, suggesting ongoing viral evolution and quasispecies replacement over time. They saw evidence of early pressure driving net evolution away from a computationally reconstructed common ancestor, known as Bole1b, in predicted CTL epitopes and E1E2, with balanced evolution toward and away from the Bole1b amino acid sequence in the remainder of the genome. Late in chronic infection, the rate of evolution toward the Bole1b sequence increased, resulting in net neutral evolution relative to Bole1b across the entire 5.2-kb hemigenome. Surprisingly, even late in chronic infection, net amino acid evolution away from the infecting inoculum sequence still could be observed. These data suggest that, late in chronic infection, ongoing HCV evolution is not random genetic drift but rather the product of strong pressure toward a common ancestor and concurrent net ongoing evolution away from the inoculum virus sequence, likely balancing replicative fitness and ongoing immune escape. Bailey JR, Laskey S, Wasilewski LN, Munshaw S, Fanning LJ, Kenny-Walsh E, Ray SC. Constraints on viral evolution during chronic hepatitis C virus infection arising from a common-source exposure. J Virol. 2012 Dec; 86(23): 12582-12590.

Risky Alcohol Use and Serum Aminotransferase Levels in HIV-Infected Adults with and Without Hepatitis C The purpose of this study was to examine the association between risky drinking amounts and serum aminotransferase levels in HIV-infected adults with and without hepatitis C virus (HCV) infection. In a prospective cohort of HIV-infected adults with current or past alcohol problems, the authors assessed whether drinking risky amounts (as defined by the National Institute on Alcohol Abuse and Alcoholism) was associated with higher levels of serum aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) over time, stratifying analyses by HCV status. Generalized linear mixed effects regression models were used to examine the association between risky drinking and natural log-transformed AST and ALT over time. Among HIV/HCV-coinfected persons (n = 200), risky drinking was associated with a higher adjusted mean AST (62.2 vs. 51.4 U/L; adjusted ratio of means 1.2, 95% CI [1.07, 1.37], p = .003) and ALT (51.3 vs. 41.6 U/L; adjusted ratio of means 1.2, 95% CI [1.07, 1.42], p = .004) compared with non-risky drinking. In contrast, among HIV-infected adults without HCV infection (n = 197), there were no significant differences between those who did and did not drink risky amounts in

AST (34.7 vs. 33.3 U/L; adjusted ratio of means = 1.0, 95% CI [0.95, 1.14], p = .36) or ALT (29.1 vs. 28.7 U/L; adjusted ratio of means = 1.0, 95% CI [0.91, 1.13], p = .78). Among HIV-infected adults with HCV, those who drink risky amounts have higher serum aminotransferase levels than those who do not drink risky amounts. These results suggest that drinking risky amounts may be particularly harmful in HIV/HCV-coinfected adults and supports recommendations that providers pay special attention to drinking in this population. Tsui JI, Cheng DM, Libman H, Bridden C, Saitz R, Samet JH. Risky alcohol use and serum aminotransferase levels in HIV-infected adults with and without hepatitis C. J Stud Alcohol Drugs. 2013 Mar; 74(2): 266-270.

An Epidemiologic Update on Hepatitis C Infection in Persons Living with or at Risk of HIV Infection Due to shared routes of transmission, coinfection with both human immunodeficiency virus type 1 (HIV-1) and hepatitis C virus (HCV) is relatively common and results in accelerated liver disease, driving morbidity and mortality. Deaths related to HCV now exceed deaths related to HIV in the United States, and co-infected patients bear a significant proportion of that mortality. This burden may be addressed by novel antiviral therapies that promise increased rates of cure or by enhanced access to liver transplantation, but these are costly interventions. Ultimately, the future burden of coinfection is addressed by greater understanding of who is at risk for development of each infection, thus guiding preventive efforts. Key recent reports regarding the US burden of morbidity and mortality due to HCV and groups at risk for coinfection are reviewed, with a focus on recently described HCV occurring among young injection drug users and men who have sex with men. Given the lack of available vaccine against HCV, enhanced detection and surveillance is a vital component of our public health strategy to combat HCV. Kim AY, Onofrey S, Church DR. An epidemiologic update on hepatitis C infection in persons living with or at risk of HIV infection. J Infect Dis. 2013 Mar; 207 Suppl 1: S1-6.

Immunosensor with Fluid Control Mechanism for Salivary Cortisol Analysis The purpose of this research is to demonstrate a new design for a cortisol immunosensor for the noninvasive and quantitative analysis of salivary cortisol. We propose a cortisol immunosensor with a fluid control mechanism which has both a vertical flow and a lateral flow. The detected current resulting from a competitive reaction between the sample cortisol and a glucose oxidase (GOD)-labeled cortisol conjugate was found to be inversely related to the concentration of cortisol in the sample solution. A calibration curve using the relative detected current showed a R(2)=0.98 and CV=14% for a range of standard cortisol solutions corresponding to the concentrations of native salivary cortisol (0.1-10 ng/ml). The measurement could be accomplished within 35 min and the cortisol immunosensor could be reused. These results show promise for realizing an on-site and easy-to-use biosensor for cortisol. Used for evaluation of human salivary cortisol levels, the cortisol immunosensor measurement corresponded closely with commercially available ELISA method (R(2)=0.92). Our results indicate the promise of the new cortisol immunosensor for noninvasive, point of care measurement of human salivary cortisol levels. Yamaguchi M, Matsuda Y, Sasaki S, Sasaki M, Kadoma Y, Imai Y, Niwa D, Shetty V. Immunosensor with fluid control mechanism for salivary cortisol analysis. Biosens Bioelectron. 2013 Mar 15;41:186-91.

Ethnic Group Differences in Cardiometabolic Disease Risk Factors Independent of Body Mass Index Among American Youth The purpose of this analysis was to identify any ethnic group differences in the prevalence of cardiometabolic disease risk factors independent of body mass index (BMI) in United States youth. Data on 3,510 boys and girls ages 8-to-11 years old from the 1999-2008 National Health and Nutrition Examination Surveys were analyzed to determine the prevalence of one or ≥ 3 cardiometabolic disease risk factors: abnormal waist circumference and

systolic (SBP) and diastolic blood pressure (DBP), increased concentrations of fasting triglyceride and decreased concentrations of high density lipoprotein (HDL) cholesterol before and after adjusting for BMI. Abnormal waist circumference and HDL-cholesterol significantly differed by ethnic group before and after adjusting for BMI ($P<0.01$). Non-Hispanic blacks were significantly less likely to have abnormal HDL cholesterol concentrations than were Hispanics and non-Hispanic whites, but non-Hispanic whites were significantly more likely to have elevated triglycerides and three or more abnormal cardiometabolic risk factors than non-Hispanic blacks. These findings point to ethnic group disparities not related to BMI alone, even in children as young as 8-to-11 years old. Programs to prevent and treat eventual cardiometabolic disease in children could be tailored for specific ethnic backgrounds as a result. Messiah SE, Arheart KL, Lopez-Mitnik G, Lipshultz SE, Miller TL. Ethnic group differences in cardiometabolic disease risk factors independent of body mass index among american youth. Obesity (Silver Spring). 2013 Mar 1.

SERVICES RESEARCH

Medication Assisted Treatment in US Drug Courts: Results from a Nationwide Survey of Availability, Barriers and Attitudes Drug treatment courts are an increasingly important tool in reducing the census of those incarcerated for non-violent drug offenses; medication assisted treatment (MAT) is proven to be an effective treatment for opioid addiction. However, little is known about the availability of and barriers to MAT provision for opioid-addicted people under drug court jurisdiction. Using an online survey, the authors assessed availability, barriers, and need for MAT (especially agonist medication) for opioid addiction in drug courts. Ninety-eight percent reported opioid-addicted participants, and 47% offered agonist medication (56% for all MAT including naltrexone). Barriers included cost and court policy. Responses revealed significant uncertainty, especially among non-MAT providing courts. Political, judicial and administrative opposition appear to affect MAT's inconsistent use and availability in drug court settings. These data suggest that a substantial, targeted educational initiative is needed to increase awareness of the treatment and criminal justice benefits of MAT in the drug courts. Matusow H, Dickman S, Rich J, Fong C, Dumont D, Hardin C, Marlowe D, Rosenblum A. Medication assisted treatment in US drug courts: Results from a nationwide survey of availability, barriers and attitudes. J Subst Abuse Treat. 2012.

Perceived Unmet Need for Alcohol and Drug Use Treatments and Future Use of Services: Results from a Longitudinal Study This study assessed the association of perceived need for and perceived barriers to treatments for substance use disorder (SUD) with subsequent use of these treatments in community settings. Drawing on data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), the authors examined the association of perceived need and barriers to SUD treatments in waves 1 of NESARC (2001-2002; n=43,093) with the subsequent use of these treatments in the follow-up wave 2 (2004-2005; n=34,625). Only 8.5% (n=195) of the 2333 NESARC participants with an untreated 12-month SUD in wave 1 perceived a need for SUD treatment. Participants who reported a perceived need were more likely to use these services in follow-up than those who did not report such a need (14.8% vs. 4.9%, adjusted odds ratio [aOR]=3.16, 95% confidence intervals [CI]=1.70-5.90, P<0.001). Among participants who perceived a need, those who reported pessimistic attitudes towards treatments as a barrier were less likely than others to use services in follow-up (aOR=0.08, 95% CI=0.01-0.73, P=0.027). Other barriers, including financial barriers and stigma were not significantly associated with treatment seeking. The findings suggest the need for a two-pronged approach to improving treatment seeking for SUD in community settings: one focusing on enhancing recognition of these disorders, the other focusing on educating potential consumers regarding the benefits of SUD treatments. Mojtabai R, Crum R. Perceived unmet need for alcohol and drug use treatments and future use of services: Results from a longitudinal study. Drug Alcohol Depend. 2013; 127(1-3): 59-64.

Toward a More Systematic Assessment of Smoking: Development of a Smoking Module for PROMIS® The aim of the PROMIS® Smoking Initiative is to develop, evaluate, and standardize item banks to assess cigarette smoking behavior and biopsychosocial constructs associated with smoking for both daily and non-daily smokers. The authors used qualitative methods to develop the item pool (following the PROMIS® approach: e.g., literature search, “binning and winnowing” of items, and focus groups and cognitive interviews to finalize wording and format), and quantitative methods (e.g., factor analysis) to develop the item banks. They considered a total of 1,622 extant items, and 44 new items for inclusion in the smoking item banks. A final set of 277 items representing 11 conceptual domains was selected for field testing in a national sample of smokers.

Using data from 3,021 daily smokers in the field test, an iterative series of exploratory factor analyses and project team discussions resulted in six item banks: Positive Consequences of Smoking (40 items), Smoking Dependence/Craving (55 items), Health Consequences of Smoking (26 items), Psychosocial Consequences of Smoking (37 items), Coping Aspects of Smoking (30 items), and Social Factors of Smoking (23 items). The authors conclude that inclusion of a smoking domain in the PROMIS® framework will standardize measurement of key smoking constructs using state-of-the-art psychometric methods, and make them widely accessible to health care providers, smoking researchers and the large community of researchers using PROMIS® who might not otherwise include an assessment of smoking in their design. Next steps include reducing the number of items in each domain, conducting confirmatory analyses, and duplicating the process for non-daily smokers. Edelen M, Tucker J, Shadel W, Stucky B, Cai L. Toward a more systematic assessment of smoking: Development of a smoking module for PROMIS®. Addict Behav. 2012; 37(11): 1278-1284.

Probability and Predictors of Treatment-Seeking for Prescription Opioid Use Disorders: A National Study Prescription opioid use disorders are the second most common drug use disorder behind only cannabis use disorders. Despite this, very little is known about the help-seeking behavior among individuals with these disorders. The sample included respondents of the Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) with a lifetime diagnosis of prescription drug use disorders (N=623). Unadjusted and adjusted hazard ratios are presented for time to first treatment-seeking by socio-demographic characteristics and comorbid psychiatric disorders. The lifetime cumulative probability of treatment seeking was 42% and the median delay from prescription drug use disorder onset to first treatment was 3.83 years. Having an earlier onset of prescription opioid use disorder and a history of bipolar disorder, major depression disorder, specific phobia and cluster B personality disorders predicted shorter delays to treatment. Although some comorbid psychiatric disorders increase the rate of treatment-seeking and decrease delays to first-treatment contact rates of treatment-seeking for prescription drug use disorder are low, even when compared with rates of treatment for other substance use disorders. Given the high prevalence and adverse consequences of prescription drug use disorder, there is a need to improve detection and treatment of prescription opioid use disorder. Blanco C, Iza M, Schwartz R, Rafful C, Wang S, Olfson M. Probability and predictors of treatment-seeking for prescription opioid use disorders: A National Study. Drug Alcohol Depend. 2013.

HIV Rapid Testing with Information Only in Substance Abuse Treatment Programs is Cost Effective Compared with Off-Site Referral The President's National HIV/AIDS Strategy calls for coupling HIV screening and prevention services with substance abuse treatment programs. Fewer than half of US community-based substance abuse treatment programs make HIV testing available on-site or through referral. The authors measured the cost-effectiveness of three HIV testing strategies evaluated in a randomized trial conducted in 12 community-based substance abuse treatment programs in 2009: off-site testing referral, on-site rapid testing with information only, on-site rapid testing with risk-reduction counseling. Data from the trial included patient demographics, prior testing history, test acceptance and receipt of results, undiagnosed HIV prevalence (0.4%) and program costs. The Cost-Effectiveness of Preventing AIDS Complications (CEPAC) computer simulation model was used to project life expectancy, lifetime costs, and quality-adjusted life years (QALYs) for HIV-infected individuals. Incremental cost-effectiveness ratios (2009 US $/QALY) were calculated after adding costs of testing HIV-uninfected individuals; costs and QALYs were discounted at 3% annually. Referral for off-site testing is less efficient (dominated) compared to offering on-site testing with information only. The cost-effectiveness ratio for on-site testing with

information is $60,300/QALY in the base case, or $76,300/QALY with 0.1% undiagnosed HIV prevalence. HIV risk-reduction counseling costs $36 per person more without additional benefit. The authors conclude that a strategy of on-site rapid HIV testing offer with information only in substance abuse treatment programs increases life expectancy at a cost-effectiveness ratio <$100,000/QALY. Policymakers and substance abuse treatment leaders should seek funding to implement on-site rapid HIV testing in substance abuse treatment programs for those not recently tested. Schackman B, Metsch L, Colfax G, Leff J, Wong A, Scott C, Feaster D, Gooden L, Matheson T, Haynes L, Paltiel A, Walensky R. The cost-effectiveness of rapid HIV testing in substance abuse treatment: Results of a randomized trial. Drug Alcohol Depend. 2012.

A Quasi-Experimental Study Examining New York State's Tobacco-Free Regulation: Effects on Clinical Practice Behaviors On July 24, 2008, New York State (NYS) became the first state to require all state-funded or state-certified substance use disorder (SUD) treatment organizations to be 100% tobacco-free and offer tobacco cessation (TC) treatment. The current study used a quasi-experimental, non-equivalent control group design with a pretest and posttest to examine the effect of the NYS tobacco-free regulation on three clinical practice behaviors (use of TC-related intake procedures, use of guideline recommended counseling for TC, and pharmacotherapy availability) in a diverse sample of SUD treatment programs. Repeated cross sectional data were collected from NYS counselors (experimental group) and non-NYS counselors (control group) approximately 4 months pre-regulation (N = 282 and 659, respectively) and 10-12 months post-regulation (N = 364 and 733, respectively). Using mixed-effects models, results at pre-regulation indicate no group differences in the three clinical practice behaviors. However, significant post-regulation effects were found such that the experimental group reports greater use of TC-related intake procedures, guideline recommended counseling, and availability of pharmacotherapy than the control group. Additionally, the experimental but not the control group shows increases in all three clinical practice behaviors from pre-regulation to post-regulation. The authors conclude that the NYS tobacco-free regulation had a significant and positive effect on promoting patient TC efforts among counselors. Eby LT, Laschober TC. A quasi-experimental study examining New York State's tobacco-free regulation: Effects on clinical practice behaviors. Drug Alcohol Depend. 2013; epub ahead of print e1-e7.

Perceived Implementation of The Office of Alcoholism and Substance Abuse Services (OASAS) Tobacco-Free Regulation in NY State and Clinical Practice Behaviors to Support Tobacco Cessation: A Repeated Cross-Sectional Study This study measured substance use disorder clinicians' perceptions regarding the implementation extensiveness of the Office of Alcohol and Substance Abuse Services (OASAS) tobacco-free regulation, passed in New York State in July of 2008, at three time-points and across organizations with varying characteristics. Repeated cross-sectional data were collected from clinicians approximately 4 months pre-regulation (time 0, n=362), 10-12 months post-regulation (time 1, n=462), and 20-24 months post-regulation (time 2, n=509). Clinician perceptions of implementation extensiveness (number of required policies in effect), use of tobacco cessation-related intake procedures, and use of guideline recommended counseling for treating tobacco dependence are significantly greater at time 1 and time 2 compared to time 0. Additionally, differences are found in perceived implementation extensiveness based on hospital-based status, profit status, and level of care offered, although the pattern of effects differed some over the three time-points under investigation. Eby LT, Laschober TC. Perceived Implementation Of The Office Of Alcoholism And Substance Abuse Services (OASAS) Tobacco-Free Regulation In NY state and clinical practice behaviors to support tobacco cessation: A repeated cross-sectional study. J Subst Abuse Treat. 2013; epub ahead of print e1-e8.

A Qualitative Examination of the Positive and Negative Consequences Associated with Going Tobacco-Free in Substance Abuse Treatment: The NY State Experience In 2008, the New York State (NYS) Office of Alcoholism and Substance Abuse Services (OASAS) required all state-funded or state-certified addiction treatment programs to be 100% tobacco-free. The regulation prohibits the use or possession of all tobacco products by patients, employees, volunteers, and visitors. This includes exterior grounds and vehicles owned, leased, or operated by the facility. Addiction treatment centers are also required to screen patients for tobacco use and incorporate tobacco cessation into treatment programming. This study examined the perceived effectiveness of this regulation from the perspective of counselors and clinical supervisors. Qualitative data were collected from 261 counselors and 80 clinical supervisors working in 50 free-standing substance abuse treatment programs throughout NYS. Questions asked about the perceived positive and negative consequences of the OASAS regulation approximately 1 year after its implementation. The findings indicate mixed reactions to the regulation. A wide range of positive and negative consequences were identified, which were generally consistent across counselor and clinical supervisor reports. The most commonly reported positive outcomes were positive behavior change (e.g., less smoking, increased intentions to quit) and increased awareness about smoking (e.g., dangers, available assistance to quit). The most commonly reported negative consequences were reinforcing addict behaviors among patients (e.g., lying, "dealing" cigarettes) and enforcement problems (e.g., difficulty enforcing, policing for compliance). Findings have implications for the implementation of tobacco-free regulations in substance abuse treatment programs. Eby LT, Sparks TE, Evans E, Selzer JA. A qualitative examination of the positive and negative consequences associated with going tobacco-free in substance abuse treatment: The NY State experience. Nicotine Tob Res. 2012; 14(12): 1407-1417.

Going Tobacco-Free: Predictors of Clinician Reactions and Outcomes of The NY State Office of Alcoholism and Substance Abuse Services Tobacco-Free Regulation In an effort to reduce patient tobacco dependence and create healthier work environments, New York State (NYS) mandated 100% tobacco-free addiction treatment programs for state funded or certified facilities in 2008. The authors present the results of a longitudinal study examining how local implementation features shape clinician reactions to the regulation and influence post-regulation clinician behavior and strain. A cohort of 147 clinicians associated with 13 treatment organizations throughout NYS completed a survey prior to the passage of the regulation and again approximately 1year post-regulation. Findings reveal that local implementation features of clinician participation in the planning for change, the provision of change-related information, and perceived organizational support predicted perceptions of change management fairness, which in turn predicted clinical practice behaviors to support smoking cessation, as well as psychological and behavioral strain. In contrast, self-efficacy for change was neither related to local implementation nor clinician outcomes. Practical implications are discussed. Eby LT, George K, Brown BL. Going tobacco-free: Predictors of clinician reactions and outcomes of the NY State Office Of Alcoholism And Substance Abuse Services Tobacco-Free Regulation. J Subst Abuse Treat. 2013; 44: 280-287.

Trends and Disparities in Antiretroviral Therapy Initiation and Virologic Suppression among Newly Treatment-Eligible HIV-Infected Individuals in North America, 2001-2009 Since the mid-1990s, effective antiretroviral therapy (ART) regimens have improved in potency, tolerability, ease of use, and class diversity. The authors sought to examine trends in treatment initiation and resulting human immunodeficiency virus (HIV) virologic suppression in North America between 2001 and 2009, and demographic and geographic disparities in these outcomes. They analyzed data on HIV-infected individuals newly clinically eligible for ART (ie, first reported CD4(+) count <350

cells/μL or AIDS-defining illness, based on treatment guidelines during the study period) from 17 North American AIDS Cohort Collaboration on Research and Design cohorts. Outcomes included timely ART initiation (within 6 months of eligibility) and virologic suppression (d500 copies/mL, within 1 year).The authors examined time trends and considered differences by geographic location, age, sex, transmission risk, race/ethnicity, CD4(+) count, and viral load, and documented psychosocial barriers to ART initiation, including non-injection drug abuse, alcohol abuse, and mental illness. Among 10,692 HIV-infected individuals, the cumulative incidence of 6-month ART initiation increased from 51% in 2001 to 72% in 2009 (P(trend) >< .001). The cumulative incidence of 1-year virologic suppression increased from 55% to 81%, and among ART initiators, from 84% to 93% (both P(trend) < .001). A greater number of psychosocial barriers were associated with decreased ART initiation, but not virologic suppression once ART was initiated. The authors found significant heterogeneity by state or province of residence (P < .001). In the last decade, timely ART initiation and virologic suppression have greatly improved in North America concurrent with the development of better-tolerated and more potent regimens, but significant barriers to treatment uptake remain, both at the individual level and systemwide. Hanna D, Buchacz K, Gebo K, Hessol N, Horberg M, Jacobson L, Kirk G, Kitahata M, Korthuis P, Moore R, Napravnik S, Patel P, Silverberg M, Sterling T, Willig J, Lau B, Althoff K, Crane H, Collier A, Samji H, Thorne J, Gill M, Klein M, Martin J, Rodriguez B, Rourke S, Gange S, Gange S. Trends and disparities in antiretroviral therapy initiation and virologic suppression among newly treatment-eligible HIV-infected individuals in North America, 2001-2009. Clin Infect Dis. 2013; 1-10.

Probability and Predictors of Remission from Life-Time Prescription Drug Use Disorders: Results from The National Epidemiologic Survey on Alcohol and Related Conditions While prescription drug use disorders (PDUD) has become an important and growing public health problem, little is known about their course. This study aims to estimate cumulative probability of remission from sedatives, tranquilizers, opioids and stimulants, and to identify predictors of remission across substances. Analyses were done for the sub-sample of individuals with lifetime history of abuse or dependence on sedatives (n = 402), tranquilizers (n = 372), opioids (n = 521), and stimulants (n = 765) at Wave 1 of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). Cumulative probability estimates and hazard ratios for remission from PDUD were obtained for the general population. Lifetime cumulative probability estimates of remission were above 96% for all substances assessed. Half of the cases of PDUD remitted between 4 and 5 years after onset. Remission from PDUD was greater for younger individuals. Males exhibited lower hazards of remission for stimulants use disorder. A diagnosis of personality disorders decreased probability of remission for sedatives and stimulants. Only abuse or dependence on some prescription drugs decreased the probability of remission from other PDUD, whereas other drug disorders did not predict remission. A significant proportion of individuals with PDUD achieve remission at some point in their life-time. Predictors of remission were found to be mostly substance-specific rather than common across substances. The lower rates of remission among some subgroups of the population highlight the need to strengthen preventive and intervention efforts among vulnerable population subgroups. Blanco C, Secades-Villa R, García-Rodríguez O, Labrador-Mendez M, Wang S, Schwartz R. Probability and predictors of remission from life-time prescription drug use disorders: Results From The National Epidemiologic Survey On Alcohol And Related Conditions. J Psychiatr Res. 2013; 47(1): 42-49.

Primary Care Provider Cultural Competence and Racial Disparities in HIV Care and Outcomes Health professional organizations have advocated for increasing the "cultural competence" (CC) of healthcare providers, to reduce racial and ethnic disparities in patient care. It is unclear whether provider CC is associated with more equitable care. To evaluate whether provider CC is associated with quality of care and outcomes for patients with HIV/AIDS the authors conducted a survey of 45 providers and 437 patients at four urban HIV clinics in the U.S. Providers' self-rated CC was measured using a novel, 20-item instrument. Outcome measures included patients' receipt of antiretroviral (ARV) therapy, self-efficacy in managing medication regimens, complete 3-day ARV adherence, and viral suppression. Providers' mean age was 44 years; 56 % were women, and 64 % were white. Patients' mean age was 45; 67 % were men, and 77 % were nonwhite. Minority patients whose providers scored in the middle or highest third on self-rated CC were more likely than those with providers in the lowest third to be on ARVs, have high self-efficacy, and report complete ARV adherence. Racial disparities were observed in receipt of ARVs (adjusted OR, 95 % CI for white vs. nonwhite: 6.21, 1.50-25.7), self-efficacy (3.77, 1.24-11.4), and viral suppression (13.0, 3.43-49.0) among patients of low CC providers, but not among patients of moderate and high CC providers (receipt of ARVs: 0.71, 0.32-1.61; self-efficacy: 1.14, 0.59-2.22; viral suppression: 1.20, 0.60-2.42). Provider CC was associated with the quality and equity of HIV care. These findings suggest that enhancing provider CC may reduce racial disparities in healthcare quality and outcomes. Saha S, Korthuis P, Cohn J, Sharp V, Moore R, Beach M. Primary care provider cultural competence and racial disparities in HIV care and outcomes. J Gen Intern Med. 2013; 1-9.

Patient and Provider Comfort Discussing Substance Use Substance use is a prevalent issue in primary care with wide-reaching implications, particularly for the care of HIV-infected patients. This analysis identified patient and provider characteristics associated with high comfort discussing substance use in HIV primary care clinics using multivariable logistic regression. A total of 413 patients and 44 providers completed surveys on their comfort discussing substance use. Additional independent variables from surveys included demographics, drug and alcohol use, self-efficacy, and activation for patients. Provider-level data included demographics, training, practice descriptors, and stress levels. The majority of patients (76%) and providers (73%) reported high comfort. In multivariable analysis, patients with current problematic alcohol use or current drug use were half as likely to report high comfort compared to their non-substance-using peers. Higher patient self-efficacy and high levels of patient activation were independently associated with increased odds of high patient comfort. While provider-level characteristics were not associated with provider comfort, the types of patients a provider saw were. Namely, the proportion of patients on antiretroviral therapy was inversely associated with the odds of high provider comfort, whereas the proportion of patients with high patient activation was positively associated. Patients likely to benefit from a discussion of substance use, those with current use, are the least likely to report comfort discussing that use. Interventions that increase patient activation or self-efficacy may also increase their comfort. This research guides future interventions to increase the prevalence of discussions on substance use. Ray M, Beach M, Nicolaidis C, Choi D, Saha S, Korthuis P. Patient and provider comfort discussing substance use. Fam Med. 2013; 45(2): 109-117.

Predictors of Quit Attempts and Successful Quit Attempts in a Nationally Representative Sample of Smokers Although most current smokers report that they would like to quit, most quit attempts fail suggesting that predictors of quitting attempts may differ from those of successful attempts. The authors examined socio-demographic and clinical predictors of quit attempts and successful quit attempts in a nationally representative sample of US adults. Data was collected in

2001-2002 (Wave 1) and 2004-2005 (Wave 2). Almost 40% of individuals who had not previously attempted to quit, tried to quit over the next three years; only 4.6% of those who tried had succeeded at the time of the evaluation. Hispanics, Asians, individuals with high income, and those with college education were less likely to attempt to quit, whereas those with daily nicotine use, younger age at first use and most symptoms of dependence were more likely to do so. Having an educational level below high school and older age at first nicotine use were predictors of successful quitting. Despite relatively high rates of quit attempts, rates of success are extremely low, indicating a gap between the public health need of decreasing tobacco use, and existing means to achieve it. Although there is a need to encourage people to quit tobacco, there may be an equally large need to develop more effective interventions that increase the rate of successful quit attempts. Rafful C, García-Rodríguez O, Wang S, Secades-Villa R, Martínez-Ortega J, Blanco C. Predictors of quit attempts and successful quit attempts in a nationally representative sample of smokers. Addict Behav. 2013; 38(4): 1920-1923.

Integrating Buprenorphine Maintenance Therapy into Federally Qualified Health Centers: Real-World Substance Abuse Treatment Outcomes Few studies have examined real-world effectiveness of integrated buprenorphine maintenance treatment (BMT) programs in federally qualified health centers (FQHCs). Opioid dependent patients (N=266) inducted on buprenorphine between July 2007 and December 2008 were retrospectively assessed at Connecticut's largest FQHC network. Six-month BMT retention and opioid-free time were collected longitudinally from electronic health records; 136 (51.1%) of patients were followed for at least 12 months. Participants had a mean age of 40.1 years, were primarily male (69.2%) and treated by family practitioners (70.3%). Co-morbidity included HCV infection (59.8%), mood disorders (71.8%) and concomitant cocaine use (59%). Retention on BMT was 56.8% at 6 months and 61.6% at 12 months for the subset observed over 1 year. Not being retained on BMT at 12 months was associated with cocaine use (AOR=2.18; 95% CI=1.35-3.50) while prescription of psychiatric medication (AOR=0.36; 95% CI 0.20-0.62) and receiving on-site substance abuse counseling (AOR=0.34; 95% CI 0.19, 0.59) improved retention. Two thirds of the participants experienced at least one BMT gap of 2 or more weeks with a mean gap length of 116.4 days. Integrating BMT in this large FQHC network resulted in retention rates similarly reported in clinical trials and emphasizes the need for providing substance abuse counseling and screening for and treating psychiatric comorbidity. Haddad M, Zelenev A, Altice F. Integrating buprenorphine maintenance therapy into federally qualified health centers: real-world substance abuse treatment outcomes. Drug Alcohol Depend. 2013: 1-9.

Post-Release Substance Abuse Outcomes among HIV-Infected Jail Detainees: Results from a Multisite Study HIV-infected individuals with substance use disorders have a high prevalence of medical and psychiatric morbidities that complicate treatment. Incarceration further disrupts healthcare access and utilization. Without appropriate diagnosis and treatment, drug relapse upon release exceeds 85%, which contributes to poor health outcomes. A prospective cohort of 1,032 HIV-infected jail detainees were surveyed in a ten-site demonstration project during incarceration and six-months post-release, in order to examine the effect of predisposing factors, enabling resources and need factors on their subsequent drug use. Homelessness, pre-incarceration cocaine and opioid use, and high drug and alcohol severity were significantly associated with cocaine and opioid relapse. Substance abuse treatment, though poorly defined, did not influence post-release cocaine and opioid use. An approach that integrates multiple services, simultaneously using evidence-based substance abuse, psychiatric care, and social services is needed to improve healthcare outcomes for HIV-infected persons transitioning from jails to the community. Krishnan A, Wickersham J, Chitsaz E, Springer S, Jordan A, Zaller N, Altice F. Post-release substance abuse

outcomes among HIV-infected jail detainees: Results from a multisite study. AIDS Behav. 2012; 1-9.

Concurrent Group Treatment for Hepatitis C: Implementation and Outcomes in a Methadone Maintenance Treatment Program Chronic hepatitis C virus (HCV) infection is highly prevalent among current and former drug users. However, the minority of patients enrolled in drug treatment programs have initiated HCV treatment. New models are needed to overcome barriers to care. In this retrospective study, the authors describe the implementation and outcomes of 42 patients treated in a concurrent group treatment (CGT) program. Patients participated in weekly provider-led group treatment sessions which included review of side effects; discussion of adherence and side effect management; administration of interferon injections; brief physical examination; and ended with brief meditation. Of the first 27 patients who initiated CGT, 42% achieved a sustained viral response. In addition, 87% (13/15) of genotype-1 infected patients treated with direct acting antiviral agent achieved an undetectable viral load at 24 weeks. The CGT model may be effective in overcoming barriers to treatment and improving adherence and outcomes among patients enrolled in drug treatment programs. Stein M, Soloway I, Jefferson K, Roose R, Arnsten J, Litwin A. Concurrent group treatment for Hepatitis C: Implementation and outcomes in a methadone maintenance treatment program. J Subst Abuse Treat. 2012; 43(4): 424-432.

Long-Term Follow-Up After Voluntary Human Immunodeficiency Virus/Sexually Transmitted Infection Counseling, Point-of-Service Testing, and Referral to Substance Abuse Treatment from the Emergency Department Public health initiatives have lowered human immunodeficiency virus (HIV) transmission risk associated with injection drug use in the United States, making sexual risk behaviors a greater source of transmission. Strategies are therefore needed to reduce these risk behaviors among all emergency department (ED) patients who use drugs, regardless of route of administration. Although recent articles have focused on the opportunity for early HIV detection and treatment through an array of ED screening and testing strategies, the effect of voluntary HIV testing and brief counseling (VT/C) on the sexual behaviors of out-of-treatment drug users over time has not yet been reported. From November 2004 to May 2008, the study screened 46,208 urban ED patients aged 18 to 54 years; 2,148 (4.6%) reported cocaine or heroin use within 30 days, 1,538 met eligibility criteria (Drug Abuse Severity Test [DAST] scores ≥3 and were either English- or Spanish-speaking), and 1,030 were enrolled. These data were obtained in the course of a randomized, controlled trial (Project SAFE) of a brief motivational intervention focused on reducing risky sexual behaviors. Although the intervention itself did not demonstrate any differential effect on the number or percentage of unprotected sexual acts, both control and intervention group participants received baseline VT/C and referral for drug treatment as part of the study protocol. This study is a report of a secondary analysis of cohort data to describe changes in sexual behaviors over time among drug users after the VT/C and referral. The mean (±SD) age of enrollees was 35.8 (±8.4) years; 67% were male, 39% were non-Hispanic black or African American, 41% were white non-Hispanic, and 19% were Hispanic. Half injected drugs and 53% met criteria for posttraumatic stress disorder (PTSD). At baseline testing, 8.8% were HIV-positive on enzyme-linked immunosorbent assay. Follow-ups were conducted at 6 and 12 months, with an attrition rate of 22%. Known HIV-positive patients accounted for 84 of 1,030 cases (8.1%), and 13 new cases were discovered: 7 of 946 at were discovered at the baseline contact (0.74%), 2 of 655 were discovered at 6 months (0.3%), and 4 of 706 (0.57%) were discovered at the 12-month contact. Twelve of the 13 returned for confirmatory testing and were actively enrolled in our infectious disease clinic. For all partners, there was a reduction in the percentage of unprotected sex acts over time ($p < 0.0001$), with decreases at 6 months versus baseline (odds ratio [OR] = 0.70,

95% confidence interval [CI] = 0.60 to 0.83), sustained at 12 months versus baseline (OR = 0.69, 95% CI = 0.58 to 0.82). For the outcome of percentage of sex acts while high, there was also a significant reduction over time ($p < 0.0001$), with a drop-off at 6 months versus baseline (OR = 0.31, 95% CI = 0.25 to 0.37) that was sustained at 12 months (OR vs. baseline 0.25, 95% CI = 0.20 to 0.30). In an adjusted model, male sex, older age, and HIV positivity predicted significant declines over time in the likelihood of unprotected sexual acts. Older age and higher baseline drug severity predicted significant decreases over time in the likelihood of sex acts while high. The authors conclude that voluntary testing and counseling for HIV or sexually transmitted infections, accompanied by referral to drug treatment, for this population of ED cocaine and heroin users was associated with reduction in unprotected sex acts and fewer sex acts while high. Bernstein E, Heeren T, Winter M, Ashong D, Bliss C, Madico G, Ayalew B, Bernstein J. Long-term follow-up after voluntary Human Immunodeficiency Virus sexually transmitted infection counseling, point-of-service testing, and referral to substance abuse treatment from the emergency department . Acad Emerg Med. 2012; 19(4): 386-395.

Receipt of Continuing Care May Help Control Long-Run Health Care Costs for Those Entering Outpatient Substance Abuse Treatment The importance of a continuing care approach for substance use disorders (SUDs) is increasingly being recognized. The authors' prior research found that a Continuing Care model for SUDs that incorporates 3 components (regular primary care, and specialty SUD and psychiatric treatment as needed) is beneficial to long-term remission. The study builds on this work to examine the cost implications of this model. The objectives of this study were to examine associations between receiving Continuing Care and subsequent health care costs over 9 years among adults entering outpatient SUD treatment in a private nonprofit, integrated managed care health plan. The authors also compare the results to a similar analysis of a demographically matched control group without SUDs. This was a longitudinal observational study. Measures collected over 9 years include demographic characteristics, self-reported alcohol and drug use and Addiction Severity Index, and health care utilization and cost data from health plan databases. Within the treatment sample, SUD patients receiving all components of Continuing Care had lower costs than those receiving fewer components. Compared with the demographically matched non-SUD controls, those not receiving Continuing Care had significantly higher inpatient costs (excess cost = $65.79/member-month; $P < 0.01$) over 9 years, whereas no difference was found between those receiving Continuing Care and controls. Although a causal link cannot be established between receiving Continuing Care and reduced long-term costs in this observational study, the findings reinforce the importance of access to health care and development of interventions that optimize patients receiving those services and that may reduce costs to health systems. Parthasarathy S, Chi F, Mertens J, Weisner C. The role of continuing care in 9-year cost trajectories of patients with intakes into an outpatient alcohol and drug treatment program. Med Care. 2012; 50(6): 540-546.

Simulation Suggests Regular HCV Screening with Liver Function Tests Cost Effective in HIV+ MSMs The authors used a Monte Carlo computer simulation to estimate the effectiveness and cost-effectiveness of screening for acute hepatitis C virus (HCV) infection in human immunodeficiency virus (HIV)-infected men who have sex with men. One-time screening for prevalent HCV infection was performed at the time of enrollment in care, followed by either symptom-based screening, screening with liver function tests (LFTs), HCV antibody (Ab) screening, or HCV RNA screening in various combinations and intervals. The authors considered both treatments with pegylated interferon and ribavirin (PEG/RBV) alone and with an HCV protease inhibitor. Outcome measures were life expectancy, quality-adjusted life expectancy, direct

medical costs, and cost-effectiveness, assuming a societal willingness to pay $100,000 per quality-adjusted life-year (QALY) gained. All strategies increased life expectancy (from 0.49 to 0.94 life-months), quality-adjusted life expectancy (from 0.47 to 1.00 quality-adjusted life-months), and costs (from $1,900 to $7,600), compared with symptom-based screening. The incremental cost-effectiveness ratio of screening with 6-month LFTs and a 12-month HCV Ab test, compared with symptom-based screening, was $43,700/QALY (for PEG/RBV alone) and $57,800/QALY (for PEG/RBV plus HCV protease inhibitor). The incremental cost-effectiveness ratio of screening with 3-month LFTs, compared with 6-month LFTs plus a 12-month HCV Ab test, was $129,700/QALY (for PEG/RBV alone) and $229,900/QALY (for PEG/RBV plus HCV protease inhibitor). With HCV protease inhibitor-based therapy, screening with 6-month LFTs and a 12-month HCV Ab test was the optimal strategy when the HCV infection incidence was d1.25 cases/100 person-years. The 3-month LFT strategy was optimal when the incidence was >1.25 cases/100 person-years. Screening for acute HCV infection in HIV-infected MSM prolongs life expectancy and is cost-effective. Depending on incidence, regular screening with LFTs, with or without an HCV Ab test, is the optimal strategy. Linas B, Wong A, Schackman B, Kim A, Freedberg K. Cost-effective screening for acute Hepatitis C virus infection in HIV-infected men who have sex with men. Clin Infect Dis. 2012; 55(2): 279-290.

Oregon's Parity Law Associated with Slight Increase in Use of Masters-Level Specialists for Mental Health Care "Parity" laws remove treatment limitations for mental health and substance-abuse services covered by commercial health plans. A number of studies of parity implementations have suggested that parity does not lead to large increases in utilization or expenditures for behavioral health services. However, less is known about how parity might affect changes in patients' choice of providers for behavioral health treatment. The authors compared initiation and provider choice among 46,470 Oregonians who were affected by Oregon's 2007 parity law. Oregon is the only state to have enacted a parity law that places restrictions on how plans manage behavioral health services. This approach has been adopted federally in the Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act. In 1 set of analyses, the authors assess initiation and provider choice using a difference-in-difference approach, with a matched group of commercially insured Oregonians who were exempt from parity. In a second set of analyses, they assess the impact of distance on provider choice. Overall, parity in Oregon was associated with a slight increase (0.5% to 0.8%) in initiations with masters-level specialists, and relatively little changes for generalist physicians, psychiatrists, and psychologists. Patients are particularly sensitive to distance for non-physician specialists. These results suggest that the Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act may lead to a shift in the use of non-physician specialists and away from generalist physicians. The extent to which these changes occur is likely to be contingent on the ease and accessibility of non-physician specialists. McConnell K, Gast S, McFarland B. The effect of comprehensive behavioral health parity on choice of provider. Med Care. 2012; 50(6): 527-533.

Which Elements of Improvement Collaboratives are Most Effective? Improvement collaborative's consisting of various components are used throughout healthcare to improve quality, but no study has identified which components work best. This study tested the effectiveness of different components in addiction treatment services, hypothesizing that a combination of all components would be most effective. An un-blinded cluster-randomized trial assigned clinics to one of four groups: interest circle calls (group teleconferences), clinic-level coaching, learning sessions (large face-to-face meetings), and a combination of all three. Interest circle calls functioned as a minimal intervention comparison group. Setting Outpatient addiction treatment clinics in the U.S.

Participants were 201 clinics in 5 states. Clinic data managers submitted data on three primary outcomes: waiting time (mean days between first contact and first treatment), retention (percent of patients retained from first to fourth treatment session), and annual number of new patients. State and group costs were collected for a cost-effectiveness analysis. Waiting time declined significantly for 3 groups: coaching (an average of -4.6 days/clinic, P=0.001), learning sessions (-3.5 days/clinic, P=0.012), and the combination (-4.7 days/clinic, P=0.001). The coaching and combination groups significantly increased the number of new patients (19.5%, P=0.028; 8.9%, P=0.029; respectively). Interest circle calls showed no significant effects on outcomes. None of the groups significantly improved retention. The estimated cost/clinic was $2,878 for coaching versus $7,930 for the combination. Coaching and the combination of collaborative components were about equally effective in achieving study aims, but coaching was substantially more cost effective. When trying to improve the effectiveness of addiction treatment services, clinic-level coaching appears to help improve waiting time and number of new patients while other components of improvement collaboratives (interest circles calls and learning sessions) do not seem to add further value. Gustafson D, Quanbeck A, Robinson J, Ford J, et al . Which elements of improvement collaboratives are most effective? Addiction. 2013; epub ahead of print e1-e31.

Sense of Community Among Individuals in Substance Abuse Recovery This study assessed the psychometric properties of the Perceived Sense of Community Scale (PSCS). Psychological sense of community is a construct that has been developed primarily in the field of community psychology and deals with the feelings of connectedness, group membership, and need fulfillment that members of small groups or larger communities may have toward other members. The current research explores this concept in the evaluation of Oxford Houses, residential homes designed to provide mutual support to individuals recovering from substance abuse and dependence, through the use of the PSCS. Overall, the PSCS was a multidimensional scale exhibiting a cluster of negatively phrased items with a large number of highly loading items. Within the three factor structure, two factors were nearly perfectly correlated, and neither sex nor race bias affected the initial formulation. However, sex and race were significant (but of small magnitude) covariates in a later sample, and highly reliable subscales were formulated with five items. Taken together, the PSCS was capable of performing as an acceptable measurement model in latent analysis. Stevens EB, Jason LA, Ferrari JR, Olson B, Legler R. Sense of community among individuals in substance abuse recovery. J Groups Addictions Recov. 2012; 7(1): 15-28.

Hope, Self-Esteem, and Self-Regulation: Positive Characteristics among Men and Women in Recovery Hopefulness remains unclear in relation to aspects of self-control and self-esteem among adults in substance abuse recovery. The present study explored the relationship between dispositional hope (agency and pathway) with self-esteem (self-liking, self-competency, and self-confidence) and self-regulation (impulse control and self-discipline), using a latent variable measurement model and structural equation modeling among adults (n = 601) residing in a communal living setting for persons in substance abuse recovery. Results showed that multiple dimensions of these constructs were significant as individual predictors. With persons in recovery, self-regulation included impulsivity control and self-discipline, while self-esteem reflected self-liking, competence, and a sense of self-confidence. Furthermore, both hope-pathways and hope-agency significantly related to self-control/impulse control but not self-control/discipline, and self-esteem/competency was associated with hope-pathways but not hope-agency. Ferrari JR, Stevens EB, Legler R, Jason LA. Hope, self-esteem, and self-regulation: Positive characteristics among men and women in recovery. J Community Psychol. 2012; 40(3): 292-300.

Initial Stages of Addiction Treatment for Blacks in Oklahoma Less Likely to Meet HEDIS Quaility Criteria than for Whites This study examined variations by race and ethnicity in initiation and engagement, two performance measures of treatment for substance use disorders that focus on the timely receipt of services during the early stage of substance abuse treatment. Administrative data from the Oklahoma Department of Mental Health and Substance Abuse Services were linked with facility-level information from the National Survey of Substance Abuse Treatment Services. The authors found that Black clients were least likely to initiate treatment, but no race or ethnic differences in treatment engagement were found when compared by race or ethnicity. Most client and facility characteristics ' association with initiation or engagement did not differ across racial or ethnic groups. Increased attention is needed to understand what may contribute to the differences and how to address them. This study also offers an approach that state agencies may implement for monitoring treatment quality and examining racial and ethnic disparities in substance abuse treatment services. Acevedo A, Garnick D, Lee M, Horgan C, Ritter G, Panas L, Davis S, Leeper T, Moore R, Reynolds M. Racial and ethnic differences in substance abuse treatment initiation and engagement. J Ethn Subst Abuse. 2012; 11(1): 1-21.

Method Allows for Assessment of the Sensitivity of Treatment Effect Estimates to Differential Follow-Up Rates The authors develop a new tool for assessing the sensitivity of findings on treatment effectiveness to differential follow-up rates in the two treatment conditions being compared. The method censors the group with the higher response rate to create a synthetic respondent group that is then compared with the observed cases in the other condition to estimate a treatment effect. Censoring is done under various assumptions about the strength of the relationship between follow-up and outcomes to determine how informative differential dropout can alter inferences relative to estimates from models that assume the data are missing at random. The method provides an intuitive measure for understanding the strength of the association between outcomes and dropout that would be required to alter inferences about treatment effects. The authors' approach is motivated by translational research in which treatments found to be effective under experimental conditions are tested in standard treatment conditions. In such applications, follow-up rates in the experimental setting are likely to be substantially higher than in the standard setting, especially when observational data are used in the evaluation. They test the method on a case study evaluation of the effectiveness of an evidence-supported adolescent substance abuse treatment program (Motivational Enhancement Therapy/Cognitive Behavioral Therapy-5 [MET/CBT-5]) delivered by community-based treatment providers relative to its performance in a controlled research trial. In this case study, follow-up rates in the community based settings were extremely low (54%) compared to the experimental setting (95%) giving raise to concerns about non-ignorable drop-out. Griffin B, McCaffrey D, Ramchand R, Hunter S, Suttorp M. Assessing the sensitivity of treatment effect estimates to differential follow-up rates: Implications for translational research. Health Serv Outcomes Res Methodol. 2012; 12(2-3): 84-103.

MET/CBT-5 Appears Effective When Delivered in Community Treatment Programs Though Questions Remain This study evaluates the effectiveness of motivational enhancement therapy/cognitive behavioral therapy-5 (MET/CBT-5) when delivered in community practice settings relative to standard community-based adolescent treatment. A quasi-experimental strategy was used to adjust for pretreatment differences between the MET/CBT-5 sample (n = 2,293) and those who received standard care (n = 458). Results suggest that youth who received MET/CBT-5 fared better than comparable youth in the control group on five of six 12-month outcomes. A low follow-up rate (54%) in the MET/CBT-5 sample raised concerns about nonresponse bias in the treatment effect estimates. Sensitivity analyses suggest that although modest differences in

outcomes between the MET/CBT-5 non-respondents and respondents would yield no significant differences between the two groups on two of the six outcomes, very large differences in outcomes between responders and non-responders would be required for youth receiving MET/CBT-5 to have fared better had they received standard outpatient care. Hunter S, Ramchand R, Griffin B, Suttorp M, McCaffrey D, Morral A. The effectiveness of community-based delivery of an evidence-based treatment for adolescent substance use. J Subst Abuse Treat. 2012; 43(2): 211-220.

Acculturation and Drug Use Disorders Among Hispanics in the U.S. The authors' objective was to examine the relationship between degree of acculturation across five different dimensions of acculturation and risk of drug use disorders (DUD) among US Hispanics. Data were derived from a large national sample of the US adult population, the National Epidemiological Survey on Alcohol and Related Conditions, collected using face-to-face interviews. The sample included civilian non-institutionalized U.S. population aged 18 years and older, with oversampling of Hispanics, Blacks and those aged 18-24 years. Interviews of more than 34,000 adults were conducted during 2004-2005 using the Alcohol Use Disorder and Associated Disabilities Interview Schedule - DSM-IV Version. A total of 6,359 subjects who identified themselves as Hispanics were included in this study. Acculturation measures used in this study assessed:, time spent in the U.S., age at immigration, language preference, social network composition, and ethnic identification. Among Hispanics, there was an inverse relationship between five complementary dimensions of acculturation and DUD. Moreover, this relationship showed a significant gradient across all acculturation dimensions and DUD. The prevalence of DUD increases with acculturation in Hispanics, across several measures of acculturation in a dose-response relationship. Hispanic cultural features and values exert a protective effect on risk of DUD. Preservation and promotion of Hispanic values may be an important component of preventive interventions for Hispanics. Blanco C, Morcillo C, Alegría M, Dedios M, Fernández-Navarro P, Regincos R, Wang S. Acculturation and drug use disorders among Hispanics in the U.S. J Psychiatr Res. 2013; 47(52): 226-232.

Self-Medication with Drugs among Those with Mood Disorders Associated with Increased Risk of Developing Incident Drug Dependence The objective of this study was to examine whether self-medication with drugs confers risk of comorbid mood and drug use disorders. A longitudinal, nationally representative survey was conducted by the National Institute on Alcohol Abuse and Alcoholism. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) assessed DSM-IV-TR psychiatric disorders, self-medication, and socio-demographic variables at 2 time points. A total of 34,653 adult, US participants completed both waves of the survey. Wave 1 was conducted between 2001 and 2002, and Wave 2 interviews took place 3 years later (2004-2005). Logistic regression and population attributable fractions were calculated to obtain estimates of the association between self-medication and incident disorders. Logistic regression analyses revealed that self-medication with drugs conferred a heightened risk of new-onset drug dependence among those with baseline mood disorders (adjusted odds ratio [AOR] = 7.65; 95% CI, 3.70-15.82; $P < .001$) and accounted for over 25% of incident drug dependence disorders among people with mood disorders. Among those with comorbid mood and drug use disorders at baseline, self-medication with drugs was associated with the persistence of drug abuse (AOR = 2.47; 95% CI, 1.34-4.56; $P < .01$), accounting for over one-fifth of the persistence of drug use disorders at 3-year follow-up. Self-medication with drugs among individuals with mood disorders confers substantial risk of developing incident drug dependence and is associated with the persistence of comorbid mood and drug use disorders. These results clarify a pathway that may lead to the development of mood and drug use disorder comorbidity and indicate an at-risk population, with potential points of intervention for prevention of comorbidity. Lazareck S, Robinson JA, Crum

RM, Mojtabai R, Sareen J, Bolton JM. A longitudinal investigation of the role of self-medication in the development of comorbid mood and drug use disorders: Findings from the NESARC. J Clin Psychiatry. 2012; 73 e588-e593.

Developing an Evidence-Based, Multimedia Group Counseling Curriculum Toolkit Training community-based addiction counselors in empirically supported treatments (ESTs) far exceeds the ever-decreasing resources of publicly funded treatment agencies. This feasibility study describes the development and pilot testing of a group counseling toolkit (an approach adapted from the education field) focused on relapse prevention (RP). When counselors (N = 17) used the RP toolkit after 3 hours of training, their content adherence scores on coping with craving and drug refusal skills showed significant improvement, as indicated by very large effect sizes (Cohen's d = 1.49 and 1.34, respectively). Counselor skillfulness, in the adequate-to-average range at baseline, did not change. Although this feasibility study indicates some benefit to counselor EST acquisition, it is important to note that the impact of the curriculum on client outcomes is unknown. Because a majority of addiction treatment is delivered in group format, a multimedia curriculum approach may assist counselors in applying ESTs in the context of actual service delivery. Brooks AC, DiGuiseppi G, Laudet A, Rosenwasser B. Developing an evidence-based, multimedia group counseling curriculum toolkit. J Subst Abuse Treat. 2012; 43: 178-189.

Cigarette Smoking and Onset of Mood and Anxiety Disorders The authors examined the association between regular cigarette smoking and new onset of mood and anxiety disorders. They used logistic regression analysis to detect associations between regular smoking and new-onset disorders among 34,653 participants in the longitudinal US National Epidemiologic Survey on Alcohol and Related Conditions (2001-2005). The authors used instrumental variable methods to assess the appropriateness of these models. Results showed that regular smoking was associated with an increased risk of new onset of mood and anxiety disorders in multivariate analyses ($F(df)(=5,61)=11.73$; $P<.001$). Participants who smoked a larger number of cigarettes daily displayed a trend toward greater likelihood of new-onset disorders. Age moderated the association of smoking with most new-onset disorders. The association was mostly statistically significant and generally stronger in participants aged 18 to 49 years but was smaller and mostly non-significant in older adults. The finding of a stronger association between regular cigarette smoking and increased risk of new-onset mood and anxiety disorders among younger adults suggest the need for vigorous antismoking campaigns and policy initiatives targeting this age group. Mojtabai R, Crum R. Cigarette smoking and onset of mood and anxiety disorders. Am J Public Health. Published online ahead of print January 17, 2013.

Performance Contracting and Quality Improvement in Outpatient Treatment: Effects on Waiting Time and Length of Stay The authors evaluate the effects of a performance contract (PC) implemented in Delaware in 2001 and participation in quality improvement (QI) programs on waiting time for treatment and length of stay (LOS) using client treatment episode level data from Delaware (n = 12,368) and Maryland (n = 147,151) for 1998-2006. Results of difference-in-difference analyses indicate that waiting time declined 13 days following the PC, after controlling for client characteristics and historical trends. Participation in the PC and a formal QI program was associated with a decrease of 20 days. LOS increased 22 days under the PC and 24 days under the PC and QI programs, after controlling for client characteristics. The PC and QI programs were associated with improvements in LOS and waiting time, although the authors cannot determine which aspects of the programs (incentives, training, and monitoring) resulted in these changes. Stewart M, Horgan C, Garnick D, Ritter G, McLellan A. Performance contracting and quality

improvement in outpatient treatment: Effects on waiting time and length of stay. J Subst Abuse Treat. 2013; 44(1): 27-33.

Substance Users' Perspectives on Helpful and Unhelpful Confrontation: Implications for Recovery Substance users commonly face confrontations about their use from family, friends, peers, and professionals. Yet confrontation is controversial and not well understood. To better understand the effects of confrontation the authors conducted qualitative interviews with 38 substance users (82% male and 79% White) about their experiences of being confronted. Confrontation was defined as warnings about potential harm related to substance use. Results from coded transcripts indicated that helpful confrontations were those that were perceived as legitimate, offered hope and practical support, and were delivered by persons who were trusted and respected. Unhelpful confrontations were those that were perceived as hypocritical, overtly hostile, or occurring within embattled relationships. Experiences of directive, persistent confrontation varied. Limitations of the study include a small and relatively high functioning sample. The authors conclude that contextual factors are important in determining how confrontation is experienced. Larger studies with more diverse samples are warranted. Polcin D, Mulia N, Jones L. Substance users' perspectives on helpful and unhelpful confrontation: Implications for recovery. J Psychoactive Drugs. 2012; 44(2): 144-152.

Drug-Abusing Offenders with Co-Morbid Mental Disorders: Gender Differences in Problem Severity, Treatment Participation, and Recidivism This study examined the gender differences in drug-related problems and predictors of recidivism among a sample of 1,444 offenders with co-morbid drug abuse and mental disorders participating in California's Proposition 36 Program. Background characteristics and problem severity in multiple key life areas were assessed at intake by using Addiction Severity Index, and drug treatment participation, mental health diagnoses and arrests were based on official records. Results showed that women demonstrated greater problem severity than men in family relationships, health, psychological health, and sexual and physical abuse history. Men on the other hand had greater criminal history, high rates of attention disorder, and psychotic disorder. More men than women were rearrested during the year after treatment admission. Logistic regression analyses showed that for the combined sample, male, young age, cocaine use (relative to methamphetamine), drug abuse severity, methadone treatment, arrest history and fewer prior treatment history were associated with higher recidivism at 12-month follow-up; lower education, cocaine use, and arrest history were related to women's recidivism, while young age, outpatient treatment, and arrest history were predictors of men's recidivism. Although the specific type of mental disorder did not seem to be predictive of recidivism, the high rates of mental health disorder and arrest of this population is problematic. Intervention strategies taking into consideration gender-specific problems and needs can improve outcomes for both. Du J, Huang D, Zhao M, Hser Y. Drug-abusing offenders with co-morbid mental disorders: Gender differences in problem severity, treatment participation, and recidivism. Biomed Environ Sci. 2013; 26(1): 32-39.

Patterns of Treatment Utilization and Methamphetamine Use During First 10years After Methamphetamine Initiation The study examined joint trajectories of methamphetamine (MA) use and substance abuse treatment utilization and identified differences among pattern groups for a sample of 348 treated for MA use. Results from group-based trajectory modeling showed that treatment utilization during the first 10years after initiation of MA use could be categorized into three distinctive patterns: about half the MA users have a pattern of low treatment utilization; one-fourth follow a quicker-to-treatment trajectory with higher probability of treatment during the first 5years of MA use and less treatment in the next 5years; and one-fourth have a slower-to-treatment

trajectory with more treatment during the second half of the 10-year period. Four MA use patterns were identified: consistently low use, moderate, and high use, as well as a decreasing use pattern. Periods of greater likelihood of treatment participation were associated with periods of decreasing or lower frequency of MA use. Brecht M, Lovinger K, Herbeck D, Urada D. Patterns of treatment utilization and methamphetamine use during first 10years after methamphetamine initiation. J Subst Abuse Treat. 2013.

Social Workers' Knowledge and Perceptions of Effectiveness and Acceptability of Medication Assisted Treatment of Substance Use Disorders Data from a national study of 345 privately funded, community-based substance use disorder (SUD) treatment centers were used to investigate social workers ' knowledge, perceptions of effectiveness, and perceptions of the acceptability of medication assisted treatments (MATs) for SUDs. Results reveal the importance of exposure to MATs for social workers to develop a knowledge base regarding the effectiveness of various pharmacological agents. Results also underline the importance of social workers' perceptions of effectiveness in forming opinions regarding the acceptability of the use of MATs in SUD treatment. Lastly, a 12-Step orientation toward treatment has a negative influence on social workers' opinions regarding the acceptability of MATs. Bride B, Abraham A, Kintzle S, Roman P. Social workers' knowledge and perceptions of effectiveness and acceptability of medication assisted treatment of substance use disorders. Soc Work Health Care. 2013; 52(1): 43-58.

Assessing Fidelity to Evidence-Based Practices in Usual Care: The Example of Family Therapy for Adolescent Behavior Problems This study describes a multi-method evaluation of treatment fidelity to the family therapy (FT) approach demonstrated by front-line therapists in a community behavioral health clinic that utilized FT as its routine standard of care. Study cases (N=50) were adolescents with conduct and/or substance use problems randomly assigned to routine family therapy (RFT) or to a treatment-as-usual clinic not aligned with the FT approach (TAU). Observational analyses showed that RFT therapists consistently achieved a level of adherence to core FT techniques comparable to the adherence benchmark established during an efficacy trial of a research-based FT. Analyses of therapist-report measures found that compared to TAU, RFT demonstrated strong adherence to FT and differentiation from three other evidence-based practices: cognitive-behavioral therapy, motivational interviewing, and drug counseling. Implications for rigorous fidelity assessments of evidence-based practices in usual care settings are discussed. Hogue A, Dauber S. Assessing fidelity to evidence-based practices in usual care: The example of family therapy for adolescent behavior problems. Eval Program Plann. 2012; 37C: 21-30.

Prevalence and Correlates of Child Sexual Abuse: A National Study This study examines the prevalence, correlates, and psychiatric disorders of adults with history of child sexual abuse (CSA). Data were derived from a large national sample of the US population. More than 34,000 adults 18 years and older residing in households were interviewed face-to-face in a survey conducted during the 2004-2005 period. Diagnoses were based on the Alcohol Use Disorder and Associated Disabilities Interview Schedule-Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition version. Weighted means, frequencies, and odds ratios of socio-demographic correlates and prevalence of psychiatric disorders were computed. Logistic regression models were used to examine the strength of associations between CSA and psychiatric disorders, adjusted for socio-demographic characteristics, risk factors, and other Axis I psychiatric disorders. The prevalence of CSA was 10.14% (24.8% in men and 75.2% in women). Child physical abuse, maltreatment, and neglect were more prevalent among individuals with CSA than among those without it. Adults with CSA history had significantly higher rates of any Axis I disorder and suicide attempts. The

frequency, type, and number of CSA were significantly correlated with psychopathology. The high correlation rates of CSA with psychopathology and increased risk for suicide attempts in adulthood suggest the need for a systematic assessment of psychiatric disorders and suicide risk in these individuals. The risk factors for CSA emphasize the need for health care initiatives geared toward increasing recognition and development of treatment approaches for the emotional sequelae CSA as well as early preventive approaches. Pérez-Fuentes G, Olfson M, Villegas L, Morcillo C, Wang S, Blanco C. Prevalence and correlates of child sexual abuse: A national study. Compr Psychiatry. 2013; 54(1): 16-27.

Dimensionality, Hierarchical Structure, Age Generalizability, and Criterion Validity of the GAIN's Behavioral Complexity Scale This study used Rasch measurement model criteria and traditional psychometric strategies to examine key psychometric properties of the Behavioral Complexity Scale (BCS), a widely used measure of externalizing disorders that focuses on attention deficit, hyperactivity, and conduct disorders. With a sample of 7,435 persons being screened for substance use disorders, the BCS was found to (a) be unidimensional, (b) have a hierarchical severity structure, (c) be generalizable to both youths and adults, and (d) meet hypothesized correlations with criterion variables. The BCS performed well as a unidimensional measure. The Rasch severity hierarchy of attention deficit to hyperactivity to conduct disorders provided a perspective that suggested that a dimensional measure could be used as an alternative and, in some ways, as an improvement to categorical diagnosis and common dimensional approaches. The finding of 3 low-severity conduct disorder items also supported a revision of categorical criteria, especially in substance use disorders. Conrad K, Conrad K, Mazza J, Riley B, Funk R, Stein M, Dennis M. Dimensionality, hierarchical structure, age generalizability, and criterion validity of the GAIN's Behavioral Complexity Scale. Psychol Assess. 2012; 24(4): 913-924.

A High-Resolution Analysis of Process Improvement: Use of Quantile Regression for Wait Time The objective of this article is to apply quantile regression for a high-resolution analysis of changes in wait time to treatment and assess its applicability to quality improvement data compared with least-squares regression. Data were obtained from addiction treatment programs participating in the Network for the Improvement of Addiction Treatment (NIATx). The authors used quantile regression to estimate wait time changes at 5, 50, and 95 percent and compared the results with mean trends by least-squares regression. Quantile regression analysis found statistically significant changes in the 5 and 95 percent quantiles of wait time that were not identified using least-squares regression. Quantile regression enabled estimating changes specific to different percentiles of the wait time distribution. It provided a high-resolution analysis that was more sensitive to changes in quantiles of the wait time distributions. Choi D, Hoffman KA, Kim M, McCarty D. A High resolution analysis of process improvement: Use of quantile regression for wait time. Health Serv Res. 2013; 48: 333-347.

The Relationship Between Clinician Turnover and Adolescent Treatment Outcomes: An Examination from the Client Perspective The turnover of substance use disorder (SUD) treatment staff has been assumed to adversely impact treatment effectiveness, yet only limited research has empirically examined this assumption. Representing an extension of prior organizational-level analyses of the impact of staff turnover on client outcomes, this study examined the impact of SUD clinician turnover on adolescent treatment outcomes using a client perspective. Multilevel regression analysis did reveal that relative to those adolescents who did not experience clinician turnover, adolescents who experienced both direct and indirect clinician turnover reported a significantly higher percentage of days using alcohol or drugs at 6-month

follow-up. However, clinician turnover was not found to have significant associations (negative or positive) with the other five treatment outcomes examined (e.g., substance-related problems, involvement in illegal activity). Thus, consistent with he authors' prior findings, the current study provides additional evidence that turnover of SUD clinicians is not necessarily associated with adverse treatment outcomes. Garner BR, Funk RR, Hunter BD. The relationship between clinician turnover and adolescent treatment outcomes: An examination from the client perspective. J Subst Abuse Treat. 2013; 44: 444-448.

Clinical Supervisor and Counselor Perceptions of Clinical Supervision in Addiction Treatment Little is empirically known about clinical supervision in addiction treatment. This study describes multiple domains of clinical supervision in addiction treatment from the perspectives of clinical supervisors and their counselors. Survey data were obtained from 484 matched clinical supervisor counselor dyads working in diverse addiction treatment programs across the United States. Supervisors report wide-ranging experiences and training in supervision. Counselors generally perceive their supervisors job performance as effective. Supervisors and their counselors largely differ in their perceptions of supervision practices, with supervisors reporting greater supervision given and their counselors reporting less supervision received. The implications are discussed. Laschober TC, Eby LT, Sauer JB. Clinical supervisor and counselor perceptions of clinical supervision in addiction treatment. J Addict Dis. 2012; 31: 382-388.

Examining Access to Addiction Treatment: Scheduling Processes and Barriers This paper reports on the phone scheduling systems that patients encounter when seeking addiction treatment. Researchers made a series of 28 monthly calls to 192 addiction treatment clinics to inquire about the clinics' first available appointment for an assessment. Each month, the date of each clinic's first available appointment and the date the appointment was made were recorded. During a 4-month baseline data collection period, the average waiting time from contact with the clinic to the first available appointment was 7.2 days. Clinics engaged in a 15-month quality improvement intervention in which average waiting time was reduced to 5.8 days. During the course of the study, researchers noted difficulty in contacting clinics and began recording the date of each additional attempt required to secure an appointment. On average, 0.47 callbacks were required to establish contact with clinics and schedule an appointment. Based on these findings, aspects of quality in phone scheduling processes are discussed. Most people with addiction seek help by calling a local addiction treatment clinic, and the reception they get matters. The results highlight variation in access to addiction treatment and suggest opportunities to improve phone scheduling processes. Quanbeck A, Wheelock A, Ford JH, Pulvermacher A, Capoccia V, Gustafson D. Examining access to addiction treatment: Scheduling processes and barriers. J Subst Abuse Treat. 2013; 44: 343-348.

Gender Differences in Prison-Based Drug Treatment Participation Prisons inmates have high rates of substance abuse and associated social and health problems, and a concomitant high need for drug treatment while incarcerated. Female inmates have an even greater treatment need, yet most inmates do not participate in treatment while incarcerated. Using data from a nationally representative sample of prison inmates, this article examines the impact of gender on prison treatment participation and gender differences in the factors associated with clinical treatment participation. Females were significantly more likely to participate in prison drug treatment than males, controlling for other factors. For both males and females, severity of drug problems predicted participation in treatment. For males but not females, race was associated with prison treatment participation, and among those with drug abuse or dependence, females with co-occurring mental health problems were more likely to participate in treatment. Implications for prison

assessment and treatment policies, and future research, are discussed. Houser K, Belenko S. Gender differences in prison-based drug treatment participation. Int J Offender Ther Comp Criminol. 2012; 56(5): 790-810.

Hope as a Predictor of Re-incarceration Among Mutual-Help Recovery Residents Given the rates of re-incarceration in the U.S., it is important to understand criminal justice risk and protective factors. Hope is a potentially important factor with two components-agency (goal-directed determination) and pathways (planning to meet goals) (Snyder et al., 1991). The authors conducted a secondary data analysis (n = 45) of a longitudinal survey of mutual-help recovery home residents. As hypothesized, greater global hope and agency significantly predicted lower odds for re-incarceration, and lower levels of pathways was not predictive. They relate these findings to hope theory and potential community applications. Dekhtyar M, Beasley C, Jason L, Ferrari J. Hope as a predictor of reincarceration among mutual-help recovery residents. J Offender Rehabil. 2012; 51(7): 474-483.

Timeline Historical Review of Income and Financial Transactions: A Reliable Assessment of Personal Finances The need for accurate and reliable information about income and resources available to individuals with psychiatric disabilities is critical for the assessment of need and evaluation of programs designed to alleviate financial hardship or affect finance allocation. Measurement of finances is ubiquitous in studies of economics, poverty, and social services. However, evidence has demonstrated that these measures often contain error. The authors compare the 1-week test-retest reliability of income and finance data from 24 adult psychiatric outpatients using assessment-as-usual (AAU) and a new instrument, the Timeline Historical Review of Income and Financial Transactions (THRIFT). Reliability estimates obtained with the THRIFT for Income (0.77), Expenses (0.91), and Debt (0.99) domains were significantly better than those obtained with AAU. Reliability estimates for Balance did not differ. THRIFT reduced measurement error and provided more reliable information than AAU for assessment of personal finances in psychiatric patients receiving Social Security benefits. The instrument also may be useful with other low-income groups. Black A, Serowik K, Ablondi K, Rosen M. Timeline historical review of income and financial transactions: a reliable assessment of personal finances. J Nerv Ment Dis. 2013; 201(1): 56-59.

Characteristics of Practitioners in A Private Managed Behavioral Health Plan Little is known about the practitioners in managed behavioral healthcare organization (MBHO) networks who are treating mental and substance use disorders among privately insured patients in the United States. It is likely that the role of the private sector in treating behavioral health will increase due to the recent implementation of federal parity legislation and the inclusion of behavioral health as a required service in the insurance exchange plans created under healthcare reform. Further, the healthcare reform legislation has highlighted the need to ensure a qualified workforce in order to improve access to quality healthcare, and provides an additional focus on the behavioral health workforce. To expand understanding of treatment of mental and substance use disorders among privately insured patients, this study examines practitioner types, experience, specialized expertise, and demographics of in-network practitioners providing outpatient care in one large national MBHO. Descriptive analyses used 2004 practitioner credentialing and other administrative data for one MBHO. The sample included 28,897 practitioners who submitted at least one outpatient claim in 2004. Chi-square and t-tests were used to compare findings across types of practitioners. About half of practitioners were female, 12% were bilingual, and mean age was 53, with significant variation by practitioner type. On average, practitioners report 15.3 years of experience (SD = 9.4), also with

significant variation by practitioner type. Many practitioners reported specialized expertise, with about 40% reporting expertise for treating children and about 60% for treating adolescents. Overall, these results based on self-report indicate that the practitioner network in this large MBHO is experienced and has specialized training, but echo concerns about the aging of this workforce. These data should provide us with a baseline of practitioner characteristics as we enter an era that anticipates great change in the behavioral health workforce. Reif S, Torres M, Horgan C, Merrick E. Characteristics of practitioners in a private managed behavioral health plan. BMC Health Serv Res. 2012; 12(1): 283-293.

Does Mandating Offenders to Treatment Improve Completion Rates? While it is known that community-based outpatient treatment for substance abusing offenders is effective, treatment completion rates are low and much of the prior research has been conducted with offenders in residential treatment or therapeutic communities. The aim of the present study was to assess whether offenders who are mandated to community-based outpatient treatment have better completion rates compared to those who enter treatment voluntarily. The 160 research participants were a heterogeneous group of substance abusers who were under various levels of criminal justice supervision (CJS) in the community. The participants were enrolled in an intensive outpatient program and were recruited into the study between July 2007 and October 2010. All offenders received weekly therapy sessions using a cognitive problem solving framework and 45% completed the 6month treatment program. Interestingly, those who were mandated demonstrated less motivation at treatment entry yet were more likely to complete treatment compared to those who were not court-ordered to treatment. While controlling for covariates known to be related to treatment completion, the logistic regression analyses demonstrated that court-ordered offenders were over 10 times more likely to complete treatment compared to those who entered treatment voluntarily (OR=10.9, CI=2.0-59.1, p=.006). These findings demonstrate that stipulated treatment for offenders may be an effective way to increase treatment compliance. Coviello D, Zanis D, Wesnoski S, Palman N, Gur A, Lynch K, McKay J. Does mandating offenders to treatment improve completion rates? J Subst Abuse Treat. 2013; 44(4): 417-425.

Prospective Effects of Traumatic Event Re-Exposure and Post-Traumatic Stress Disorder in Syringe Exchange Participants The aim of the study was to determine the effect of traumatic event re-exposure and post-traumatic stress disorder (PTSD) symptom severity on proximal drug use and drug abuse treatment-seeking in syringe exchange participants. Prospective longitudinal 16-month cohort study of new syringe exchange registrants enrolled in a parent study of methods to improve treatment engagement. Data were collected in a research van next to mobile syringe exchange distribution sites in Baltimore, Maryland. Male and female (n = 162) injecting drug users (IDUs) registered for syringe exchange. Traumatic event re-exposure was identified each month with the Traumatic Life Events Questionnaire. PTSD symptoms were measured with the Modified PTSD Symptom Scale-Revised, given every 4 months. Outcome measures collected monthly were days of drug use (heroin, cocaine) and drug abuse treatment-seeking behavior (interest, calls to obtain treatment, treatment participation). Each traumatic event re-exposure was associated with about 1 more day of cocaine use after accounting for the previous month's cocaine use [same month adjusted B, standard error = 1.16 (0.34); 1 month later: 0.99 (0.34)], while PTSD symptoms had no effect. Traumatic event re-exposure increased interest in drug abuse treatment [same month adjusted odds ratios with 95% confidence intervals = 1.34 (1.11-1.63)] and calling to obtain treatment [same month 1.58 (1.24-2.01); 1 month later 1.34 (1.03-1.75)]. Each 10% increase in PTSD symptom severity was associated with persistent increased interest in treatment [same month 1.25 (1.10-1.42); 1 month later 1.16 (1.02-1.32); 2 months later 1.16 (1.02-1.32)] and calling to obtain treatment

[same month 1.16 (1.02-1.32)]. Neither traumatic events nor PTSD symptoms were associated with participants receiving treatment. Becoming exposed again to traumatic events among injecting drug users is associated with an increase in cocaine use up to 1 month later, but drug use is not related to post-traumatic stress disorder symptoms. Both traumatic event re-exposure and post-traumatic stress disorder symptoms predict drug abuse treatment-seeking behavior for up to 2 months. Peirce JM, Brooner RK, Kolodner K, Schacht RL, Kidorf MS. Prospective effects of traumatic event re-exposure and post-traumatic stress disorder in syringe exchange participants. Addiction. 2013; 108(1): 148-153.

A Ban on Menthol Cigarettes: Impact on Public Opinion and Smokers' Intention to Quit The authors assessed support for a ban by the Food and Drug Administration on menthol in cigarettes and behavioral intentions among menthol smokers in the event of such a ban. They surveyed 2,649 never, former, and current smokers and used ordinal logistic regression to calculate weighted point estimates and predictors of support for a menthol ban among the adult population and menthol smokers only. For menthol smokers, they also calculated weighted point estimates and predictors of behavioral intentions. Overall, 28.2% of adults opposed, 20.0% supported, and 51.9% lacked a strong opinion about a menthol ban. Support was highest among Hispanics (36.4%), African Americans (29.0%), never smokers (26.8%), and respondents with less than a high school education (28.8%). Nearly 40% of menthol smokers said they would quit if menthol cigarettes were no longer available, 12.5% would switch to a non-menthol brand, and 25.2% would both switch and try to quit. Support for a menthol ban is strongest among populations with the highest prevalence of menthol cigarette use. A menthol ban might motivate many menthol smokers to quit. Pearson J, Abrams D, Niaura R, Richardson A, Vallone D. A ban on menthol cigarettes: Impact on public opinion and smokers' intention to quit. Am J Public Health. 2012; 102(11): e107-e114.

Costs of Alcohol Screening and Brief Intervention in Medical Settings: A Review of the Literature This article summarizes the literature on the implementation costs of alcohol screening and brief intervention (SBI) in medical settings. Electronic databases were searched using SBI- and cost-related terms. Methodological approaches and cost estimates were abstracted from each study and categorized based on the cost methodology. Costs were updated to 2009 U.S. dollars. To determine a summary cost measure, the authors excluded outliers and computed the median of the remaining cost estimates. Seventeen studies with cost estimates were identified for further study. Costs ranged from $0.51 to $601.50 per screen and from $3.41 to $243.01 per brief intervention (BI). Cost estimates were lower when an activity-based cost methodology was used, in primary care settings, and when the provider was not a doctor. The median summary cost of a screen is approximately $4, and the median summary cost of a BI is approximately $48. Screening cost estimates had more variation than BI cost estimates. Provider type and service delivery time drive the cost variation. Interpretation of cost differences was limited by insufficient reporting of the cost methodology. Cost estimates presented here are similar in size to the Healthcare Common Procedure Coding System and Current Procedural Terminology reimbursement amounts, suggesting that insurance-based service reimbursement may be sufficient to sustain alcohol SBI in practice. Bray J, Zarkin G, Hinde J, Mills M. Costs of alcohol screening and brief intervention in medical settings: A review of the literature. J Stud Alcohol Drugs. 2012; 73(6): 911-919.

Sexually Transmitted Infections Among HIV-Infected Heavy Drinkers in St Petersburg, Russia The objective of this study was to estimate the prevalence and identify correlates of four sexually transmitted infections (STIs) among HIV-infected Russians reporting heavy alcohol use and recent unprotected sex; the authors conducted a cross-sectional analysis of baseline data from

the HERMITAGE study. The primary outcome was any current STI, based on urine tests for Neisseria gonorrhoeae, Chlamydia trachomatis and Trichomonas vaginalis and serological testing for infection with Treponema pallidum. Data on potential demographic and behavioral predictors of STI were obtained from surveys administered at study entry. Of 682 participants, 12.8% (95% confidence interval [CI] 10.3, 15.3) tested positive for at least one STI. In a multivariable model adjusted for gender, age and marital status, only sex trade involvement over the last three months was significantly associated with increased odds of STI (adjusted odds ratio [AOR] 2.00, 95% CI 1.13, 3.55). Given that STIs were common in this HIV-infected cohort, and that few patient characteristics predicted STI, the current practice of screening HIV-infected Russians for syphilis alone merits re-evaluation. Pace C, Lioznov D, Cheng D, Wakeman S, Raj A, Walley A, Coleman S, Bridden C, Krupitsky E, Samet J. Sexually transmitted infections among HIV-infected heavy drinkers in St Petersburg, Russia. Int J STD AIDS. 2012; 23(12): 853-858.

Minimum Recommended Physical Activity, and Perceived Barriers and Benefits of Exercise in Methadone Maintained Persons Methadone-maintained persons are at increased risk for many physical and mental health disorders compared to the general population. Increased physical activity could offset these risks. The authors assessed physical activity level, and perceived benefits and barriers to exercise in a group of 305 methadone-maintained smokers. Mean participant age was 39.9years, 50.2% were male, 79.7% were non-Hispanic White, and mean body mass index was 29.8. Nearly 45% endorsed fair or poor physical health. Although participants perceived many benefits of exercise and few barriers, only 38% of participants met weekly recommendations for physical activity, and nearly 25% reported no physical activity. Those who met recommended guidelines were significantly more likely to endorse relapse prevention as a benefit of exercise. Motivating MMT patients to increase physical activity could have important physical, mental health, and drug treatment benefits. Caviness C, Bird J, Anderson B, Abrantes A, Stein M. Minimum recommended physical activity, and perceived barriers and benefits of exercise in methadone maintained persons. J Subst Abuse Treat. 2013; 44(4): 457-462.

Prescription Medication Exchange Patterns Among Methadone Maintenance Patients Exchange of prescription medications is a significant public health problem particularly among substance abusing populations. Little is known about the extent of medication sharing and receiving behaviors in methadone maintenance treatment (MMT) populations and the factors associated with such behaviors. The authors examined rates, and factors associated with past year medication sharing and receiving practices of 315 MMT smokers who had enrolled in a clinical trial of smoking cessation. Sequential logistic regression models estimated the effect of demographic and substance use variables on the probability of sharing or receiving medications. Participants averaged 40 years of age, and 49% were male. Among persons prescribed medications, 19.9% reported sharing. Nearly 40% had used medication not prescribed to them. Pain medications, sleep medications, and sedatives, were most commonly shared and received. Younger age was a significant predictor of both sharing medications (OR=0.92, 95%CI 0.88; 0.96, p<.01) and receiving medications (OR=0.94, 95%CI 0.92; 0.97, p<.01). Financial hardship (OR=2.05, 95%CI 1.13; 3.72, p<.05), and recent use of heroin (OR=5.59, 95%CI 1.89; 16.57, p<.01) or cocaine (OR=3.70, 95%CI 1.48; 9.28, p<.05), were also independently associated with a significantly higher likelihood of receiving prescription drugs of abuse. The high prevalence of prescription medication sharing and receiving behaviors among persons in MMT often include substances with abuse potential and suggest the need for comprehensive approaches for minimizing this phenomenon. Caviness C, Anderson B, de Dios M, Kurth M, Stein M. Prescription medication exchange patterns among methadone maintenance patients. Drug Alcohol Depend. 2013; 127(1-3): 232-238.

The Social Support and Social Network Characteristics of Smokers in Methadone Maintenance Treatment Previous studies have shown social support and social network variables to be important factors in smoking cessation treatment. Tobacco use is highly prevalent among individuals in methadone maintenance treatment (MMT). However, smoking cessation treatment outcomes in this vulnerable subpopulation have been poor and social support and social network variables may contribute. The current study examined the social support and social network characteristics of 151 MMT smokers involved in a randomized clinical trial of smoking cessation treatments. Participants were 50% women and 78% Caucasian. A high proportion (57%) of MMT smokers had spouses or partners who smoke and over two-thirds of households (68.5%) included at least one smoker. The authors' sample was characterized by relatively small social networks, but high levels of general social support and quitting support. The number of cigarettes per day was found to be positively associated with the number of smokers in the social network ($r = .239$, $p < .05$) and quitting self-efficacy was negatively associated with partner smoking ($r = -.217$, $p < .001$). Findings are discussed in the context of developing smoking cessation interventions that address the influential role of social support and social networks of smokers in MMT. de Dios M, Stanton C, Caviness C, Niaura R, Stein M. The social support and social network characteristics of smokers in methadone maintenance treatment. Am J Drug Alcohol Abuse. 2013; 39(1): 50-56.

Life 1 Year After A Quit Attempt: Real-Time Reports of Quitters and Continuing Smokers Smokers are often reluctant to quit because they fear long-lasting withdrawal. Yet little research prospectively examines smokers' withdrawal longer than 1 month post-quit. The aim of this study was to compare successful versus unsuccessful quitters' withdrawal, positive affect/pleasure, and lifestyle at 1 year post-quit. Smokers ($N = 572$) in a cessation trial completed ecological momentary assessments four times a day for 1 week pre-quit, 1 week post-quit, and 1 week at 1 year post-quit. From pre-quit to 1 year later, only quitters reported sizeable declines in craving and restlessness, and fewer stressful events. At 1 year, quitters, on average, reported no significant craving. Continuing smokers reduced their cigarette consumption considerably from pre-quit to 1 year later. Contrary to smokers' worries, long-term quitters reported less craving and restlessness than when they smoked (perhaps because cessation eliminates the acute nicotine withdrawal smokers experience between cigarettes). This information may encourage smokers to quit and endure withdrawal. Schlam T, Piper M, Cook J, Fiore M, Baker T. Life 1 year after a quit attempt: Real-time reports of quitters and continuing smokers. Ann Behav Med. 2012; 44(3): 309-319.

Impact of Broadened Coverage of Smoking Cessation Treatments on Cardiovascular Disease One third of all premature tobacco-attributable deaths are due to CVD and tobacco is the cause of approximately 15% of all CVD attributable. Primary and secondary prevention strategies that combine evidenced based tobacco dependence treatment programs along with cigarette taxes and media campaigns can result in hundreds of thousands of fewer excess deaths from smoking attributable CVD. Expanded insurance from both commercial and public insurers will be greatly expanded by the recently enacted federal health care reform but barriers to reducing the avoidable morbidity and mortality that is due to tobacco use is impacted by the potential for remaining financial barriers to full insurance coverage from Americans in regions of the country with the highest smoking prevalence rates. Fishman P. Impact of broadened coverage of smoking cessation treatments on cardiovascular disease. Curr Cardiovasc Risk Rep. 2012; 6(6): 542-548.

Relations of Alcohol Consumption With Smoking Cessation Milestones and Tobacco Dependence Alcohol consumption is associated with smoking cessation failure in both community and clinical research. However, little is known about the relation between alcohol consumption and smoking cessation milestones (i.e., achieving initial abstinence, avoiding lapses and relapse). The authors' objective in this research was to examine the relations between pretreatment alcohol consumption patterns (non/infrequent drinker, moderate drinker, binge drinker) and smoking cessation milestones and tobacco dependence. Data were collected from 1,504 smokers (58.2% women; 83.9% White; mean age = 44.67 years, SD = 11.08) making an aided smoking cessation attempt as part of a clinical trial. Alcohol consumption pattern was determined with the Composite International Diagnostic Interview. Tobacco dependence was assessed with the Wisconsin Inventory of Smoking Dependence Motives (WISDM). Alcohol consumption pattern was significantly associated with initial cessation and lapse, and these findings remained after controlling for the effects of treatment, race, gender, and cigarettes per day. Relative to moderate drinkers, both non/infrequent drinkers and binge drinkers were less likely to achieve initial cessation ($p < .05$), and binge drinkers were more likely to lapse ($p < .01$). When drinking categories were compared on tobacco dependence indices, results showed that relative to moderate drinkers, non/infrequent drinkers scored higher on several WISDM Primary Dependence Motives subscales (Tolerance, Loss of Control, and Automaticity) and binge drinkers scored higher on WISDM Secondary Dependence Motives subscales (Cue Exposure and Social-Environmental Goads). The authors conclude that non/infrequent drinkers' smoking cessation difficulties may be particularly related to core features of tobacco dependence, whereas binge drinkers' difficulties may be related to environmental and social influences. Cook J, Fucito L, Piasecki T, Piper M, Schlam T, Berg K, Baker T. Relations of alcohol consumption with smoking cessation milestones and tobacco dependence. J Consult Clin Psychol. 2012; 80(6): 1075-1085.

Epidemiology of Pain Among Outpatients in Methadone Maintenance Treatment Programs This analysis explored the prevalence and correlates of pain in patients enrolled in methadone maintenance treatment (MMT). Patients in two MMT programs starting a hepatitis care coordination randomized controlled trial completed the Brief Pain Inventory Short-Form and other questionnaires. Associations between clinically significant pain (average daily paine5 or mean pain interferencee5 during the past week), and socio-demographic data, medical status, depressive symptoms, and health-related quality of life, and current substance use were evaluated in multivariate analyses. The 489 patients included 31.8% women; 30.3% Hispanics, 29.4% non-Hispanic Blacks, and 36.0% non-Hispanic Whites; 60.1% had hepatitis C, 10.6% had HIV, and 46.8% had moderate or severe depressive symptomatology. Mean methadone dose was 95.7mg (SD 48.9) and urine drug screening (UDS) was positive for opiates, cocaine, and amphetamines in 32.9%, 40.1%, and 2.9%, respectively. Overall, 237 (48.5%) reported clinically significant pain. Pain treatments included prescribed opioids (38.8%) and non-opioids (48.9%), and self-management approaches (60.8%), including prayer (33.8%), vitamins (29.5%), and distraction (12.7%). Pain was associated with higher methadone dose, more medical comorbidities, prescribed opioid therapy, and more severe depressive symptomatology; it was not associated with UDS or self-reported substance use. Clinically significant pain was reported by almost half of the patients in MMT programs and was associated with medical and psychological comorbidity. Pain was often treated with opioids and was not associated with measures of drug use. Studies are needed to further clarify these associations and determine their importance for pain treatment strategies. Dhingra L, Masson C, Perlman D, Seewald R, Katz J, McKnight C, Homel P, Wald E, Jordan A, Young C, Portenoy R. Epidemiology of pain among outpatients in methadone maintenance treatment programs. Drug Alcohol Depend. 2013; 128(1-2): 161-165.

CTN-RELATED RESEARCH

Risk Of Methylphenidate-Induced Prehypertension In Normotensive Adult Smokers With Attention Deficit Hyperactivity Disorder The authors studied predictors of methylphenidate-induced increases in blood pressure (BP). In this secondary analysis of a randomized, double-blind, placebo-controlled smoking cessation trial, nonhypertensive adult smokers with attention deficit hyperactivity disorder randomized to osmotic-release oral system methylphenidate (OROS-MPH) (n=115) were matched one-to-one on baseline systolic BP (SBP) (±5 mm Hg) with participants randomized to placebo (n=115) and followed for 10 weeks. In adjusted mixed linear models of SBP and diastolic BP (DBP), baseline normal SBP (P<.0001) and DBP (P<.0001) were associated with significant OROS-MPH-induced increases compared with placebo, whereas significant increases were not observed in participants with baseline prehypertensive SBP (P=.27) and DBP (P=.79). Participants randomized to OROS-MPH with baseline normal BP had increased odds of developing either systolic (odds ratio [OR], 3.32; 95% confidence interval [CI], 1.41-8.37; P=.006) or diastolic prehypertension (OR, 4.32; 95% CI, 1.56-14.0; P=.004) compared with placebo using simple logistic regression. The authors demonstrated an augmented OROS-MPH-induced BP elevation and risk of prehypertension in adults with baseline normal BP. Significantly increased BP was not observed in adults with baseline prehypertension. Westover AN, Nakonezny PA, Winhusen T, Adinoff B, Vongpatanasin W. Risk of methylphenidate-induced prehypertension in normotensive adult smokers with attention deficit hyperactivity disorder. J Clin Hypertens (Greenwich). 2013 Feb; 15(2): 124-132. Epub 2012 Dec 14.

Impulsivity Is Associated With Treatment Non-Completion In Cocaine- and Methamphetamine-Dependent Patients But Differs In Nature As A Function Of Stimulant-Dependence Diagnosis Greater impulsivity, assessed by the Barratt Impulsiveness Scale-11 (BIS-11) and Stroop interference scores, has been associated with treatment completion in cocaine-dependent patients. This study evaluated the relationships among impulsivity, stimulant-dependence diagnosis, and treatment completion. Six sites evaluating 12-step facilitation for stimulant abusers obtained the BIS-11 and Stroop from 182 methamphetamine- and/or cocaine-dependent participants. Methamphetamine-dependent, relative to cocaine-dependent, participants evidenced significantly greater BIS-11 non-planning and total scores. There was a trend for poorer response inhibition, measured by the Stroop, in cocaine-dependent, relative to methamphetamine-dependent, participants. Accounting for other factors related to treatment completion, BIS-11 motor score, assessing the tendency to act without thinking, predicted treatment completion for both cocaine-dependent and methamphetamine-dependent patients. These results suggest that methamphetamine-dependent and cocaine-dependent patients may have different impulsivity profiles but that the BIS-11 may be useful in identifying both methamphetamine-dependent and cocaine-dependent patients who are at risk for treatment non-completion. Winhusen T, Lewis D, Adinoff B, Brigham G, Kropp F, Donovan DM, Seamans CL, Hodgkins CC, Dicenzo JC, Botero CL, Jones DR, Somoza E. Impulsivity is associated with treatment non-completion in cocaine- and methamphetamine-dependent patients but differs in nature as a function of stimulant-dependence diagnosis. J Subst Abuse Treat. 2013 Jan 7. [Epub ahead of print]

Gender Differences in Heterosexual Anal Sex Practices among Women and Men in Substance Abuse Treatment Heterosexual anal intercourse (HAI) is an understudied risk behavior among women and men in substance abuse treatment. Rates of HAI for women (n = 441) and men (n = 539) were identified for any, main and casual partners. More men (32.8 %) than women (27.1 %) reported engaging in HAI in the previous 90 days. These rates are higher than those

reported for both men (6.0-15.9 %) and women (3.5-13.0 %) ages 25-59 in the National Survey of Sexual Health and Behavior. Men were significantly more likely to report HAI with their casual partners (34.1 %) than women (16.7 %). In a logistic regression model generated to identify associations between HAI and variables previously shown to be related to high risk sexual behavior, being younger, bisexual, and White were significantly associated with HAI. For men, having more sex partners was also a significant correlate. HAI is a logical target for increased focus in HIV prevention interventions. Calsyn DA, Hatch-Maillette MA, Meade CS, Tross S, Campbell AN, Beadnell B. Gender differences in heterosexual anal sex practices among women and men in substance abuse treatment. AIDS Behav. 2013 Jan 16. [Epub ahead of print]

Racial/Ethnic Differences in the Rates and Correlates of HIV Risk Behaviors among Drug Abusers HIV infection disproportionately impacts minorities; yet research on racial/ethnic differences in the prevalence and correlates of HIV risk behaviors is limited. This study examined racial/ethnic differences in the rates of HIV risk behaviors and whether the relationship between HIV risk factors and HIV risk behaviors varies by race/ethnicity in clients participating in NIDA Clinical Trials Network trials. The sample was 41% non-Hispanic White, 32% non-Hispanic Black, and 27% Hispanic (N=2,063). HIV risk behaviors and measures of substance and psychosocial HIV risk factors in the past month were obtained. Non-Hispanic Blacks engaged in less HIV sexual risk behaviors overall than non-Hispanic Whites. While non-Hispanic Whites were the most likely to report any injection drug use, Hispanics engaged in the most HIV drug risk behaviors. Specific risk factors were differentially predictive of HIV risk behavior by race/ethnicity. Alcohol use severity was related to engaging in higher sex risk behaviors for non-Hispanic Blacks and Whites. Greater psychiatric severity was related to engaging in higher sex risk behaviors for non-Hispanic Whites. Drug use severity was associated with engaging in higher risk drug behaviors for non-Hispanic Whites and Hispanics with the magnitude of the relationship stronger for Hispanics. These findings highlight the need for further research testing HIV risk prevention interventions within racial/ethnic groups to identify target behaviors or risk factors that are salient to inform HIV interventions. The present study provides a systematic examination of race/ethnicity differences in the relationship between psychosocial risk factors and HIV risk behaviors. Brooks AJ, Lokhnygina Y, Meade CS, Potter JS, Calsyn DA, Greenfield SF. Racial/ethnic differences in the rates and correlates of HIV risk behaviors among drug abusers. Am J Addict. 2013 Mar; 22(2): 136-147.

Integrating Substance Abuse Care With Community Diabetes Care: Implications For Research and Clinical Practice Cigarette smoking and alcohol use are prevalent among individuals with diabetes in the US, but little is known about screening and treatment for substance use disorders in the diabetic population. This commentary discusses the scope and clinical implications of the public health problem of coexisting substance use and diabetes, including suggestions for future research. Diabetes is the seventh leading cause of death in the US, and is associated with many severe health complications like cardiovascular disease, stroke, kidney damage, and limb amputations. There are an estimated 24 million adults in the US with type 2 diabetes. Approximately 20% of adults aged 18 years or older with diabetes report current cigarette smoking. The prevalence of current alcohol use in the diabetic population is estimated to be around 50%-60% in epidemiological surveys and treatment-seeking populations. Cigarette smoking is associated with an increased risk of type 2 diabetes in a dose-dependent manner and is an independent modifiable risk factor for development of type 2 diabetes. Diabetic patients with an alcohol or other drug use disorder show a higher rate of adverse health outcomes. For example, these patients experience more frequent and severe health complications as well as an increased risk of hospitalization, and require longer hospital stays. They are also less likely to seek routine care for

diabetes or adhere to diabetes treatment than those without an alcohol or other drug use disorder. The Affordable Care Act of 2010 and the Mental Health Parity Act and Addiction Equity Act of 2008 provide opportunities for facilitating integration of preventive services and evidence-based treatments for substance use disorders with diabetes care in community-based medical settings. These laws also offer emerging areas for research. Ghitza UE, Wu LT, Tai B. Integrating substance abuse care with community diabetes care: implications for research and clinical practice. Subst Abuse Rehabil. 2013 Jan 1;4:3-10. Epub 2013 Jan 11.

Demographic and Clinical Characteristics of Middle-aged Versus Younger Adults Enrolled in a Clinical Trial of a Web-delivered Psychosocial Treatment for Substance Use Disorders
Evidence suggests that substance abuse is becoming more prevalent in middle-aged adults. The objective of this secondary analysis was to add to the growing empirical literature on the unique features of middle-aged substance abuse populations. The authors descriptively compared baseline demographic and clinical characteristics of middle-aged (age 45-62 years, n = 111) and younger (age 18-44 years, n = 395) substance abusers entering a Web-based psychosocial treatment study as part of the National Institute on Drug Abuse Clinical Trials Network. A significantly greater percentage of middle-aged adults were nonwhite and had a marital status other than single/never married. There was a significant association between frequency of Internet use and the age group. Forty-six percent of middle-aged adults versus 21% of younger adults reported no Internet use in the prior 90 days. A significantly greater percentage of middle-aged adults used cocaine, and a significantly greater percentage of younger adults used marijuana and opioids. Clinically significant cognitive impairment ($z < -1.0$) was found for the average participant in both groups on logical association of familiar concepts. This secondary analysis of a National Institute on Drug Abuse Clinical Trials Network study provides additional information on the unique features of middle-aged substance abusers. Increasing knowledge of similarities and differences between younger and middle-aged substance abusers can help with potential age-specific substance abuse treatment planning. Kalapatapu RK, Campbell A, Aharonovich E, Hu MC, Levin FR, Nunes EV. Demographic and clinical characteristics of middle-aged versus younger adults enrolled in a clinical trial of a web-delivered psychosocial treatment for substance use Disorders. J Addict Med. 2013 Jan; 7(1): 66-72.

Gender Differences In A Clinical Trial For Prescription Opioid Dependence Although gender differences in substance use disorders have been identified, few studies have examined gender differences in prescription drug dependence. The aim of this study was to examine gender differences in clinical characteristics and treatment outcomes in a large clinical trial for prescription opioid dependence. Despite no pre-treatment differences in opioid dependence severity, women reported significantly greater functional impairment, greater psychiatric severity, and higher likelihood of using opioids to cope with negative affect and pain than men. Women were also more likely than men to have first obtained opioids via a legitimate prescription and to use opioids via the intended route of administration. Men reported significantly more alcohol problems than women. There were no significant gender differences in medication dose, treatment retention, or opioid outcomes. Thus, despite the presence of pre-treatment gender differences in this population, once the study treatment was initiated, women and men exhibited similar opioid use outcomes. McHugh RK, Devito EE, Dodd D, Carroll KM, Potter JS, Greenfield SF, Connery HS, Weiss RD. J Subst Abuse Treat. 2013 Jan 10. [Epub ahead of print].

Patient Characteristics Associated With Buprenorphine/Naloxone Treatment Outcome For Prescription Opioid Dependence: Results From A Multisite Study Prescription opioid dependence is a growing problem, but little research exists on its treatment, including patient characteristics that predict treatment outcome. A secondary analysis of data from a large multisite, randomized clinical trial, the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study (POATS) was undertaken to examine baseline patient characteristics (N=360) associated with success during 12-week buprenorphine/naloxone treatment for prescription opioid dependence. Baseline predictor variables included self-reported demographic and opioid use history information, diagnoses assessed via the Composite International Diagnostic Interview, and historical opioid use and related information from the Pain And Opiate Analgesic Use History. In bivariate analyses, pre-treatment characteristics associated with successful opioid use outcome included older age, past-year or lifetime diagnosis of major depressive disorder, initially obtaining opioids with a medical prescription to relieve pain, having only used opioids by swallowing or sublingual administration, never having used heroin, using an opioid other than extended-release oxycodone most frequently, and no prior opioid dependence treatment. In multivariate analysis, age, lifetime major depressive disorder, having only used opioids by swallowing or sublingual administration, and receiving no prior opioid dependence treatment remained as significant predictors of successful outcome. This is the first study to examine characteristics associated with treatment outcome in patients dependent exclusively on prescription opioids. Characteristics associated with successful outcome after 12 weeks of buprenorphine/naloxone treatment include some that have previously been found to predict heroin-dependent patients' response to methadone treatment and some specific to prescription opioid-dependent patients receiving buprenorphine/naloxone. Dreifuss JA, Griffin ML, Frost K, Fitzmaurice GM, Potter JS, Fiellin DA, Selzer J, Hatch-Maillette M, Sonne SC, Weiss RD. Patient characteristics associated with buprenorphine/naloxone treatment outcome for prescription opioid dependence: Results from a multisite study. Drug Alcohol Depend. 2013 Jan 18. [Epub ahead of print].

Does Treatment Readiness Enhance the Response of African American Substance Users to Motivational Enhancement Therapy? The development of effective treatments for African Americans and other ethnic minorities is essential for reducing health disparities in substance use. Despite research suggesting that Motivational Enhancement Therapy (MET) may reduce substance use among African Americans, the findings have been inconsistent. This research examined the extent to which readiness-to-change (RTC) affects response to MET among African American substance users. The study was a secondary analysis of the 194 African American substance users participating in a multisite randomized clinical trial evaluating MET originally conducted within the National Drug Abuse Treatment Clinical Trials Network. The participants were randomly assigned to receive either three sessions of MET or Counseling-As-Usual (CAU) followed by the ordinary treatment and other services offered at the five participating outpatient programs. Participants were categorized as either high or lower on RTC based on their scores on the University of Rhode Island Change Assessment. The participants reported their substance use at baseline and throughout the 16 weeks after randomization. Among the high RTC participants, those in MET tended to report fewer days of substance use per week over time than participants in CAU. However, among the lower RTC participants, the CAU group tended to report fewer days of substance use over time than MET participants. In contrast to previous thinking, the findings suggest that MET may be more effective for high than lower RTC African American participants. Burlew AK, Montgomery L, Kosinski AS, Forcehimes AA. Does treatment readiness enhance the response of african american substance users to motivational enhancement therapy? Psychol Addict Behav. 2013 Feb 18. [Epub ahead of print].

Parallel Demand-Withdraw Processes in Family Therapy for Adolescent Drug Abuse
Isomorphism, or parallel process, occurs in family therapy when patterns of therapist-client interaction replicate problematic interaction patterns within the family. This study investigated parallel demand-withdraw processes in brief strategic family therapy (BSFT) for adolescent drug abuse, hypothesizing that therapist-demand/adolescent-withdraw interaction (TD/AW) cycles observed early in treatment would predict poor adolescent outcomes at follow-up for families who exhibited entrenched parent-demand/adolescent-withdraw interaction (PD/AW) before treatment began. Participants were 91 families who received at least four sessions of BSFT in a multisite clinical trial on adolescent drug abuse (Robbins et al., 2011). Prior to receiving therapy, families completed videotaped family interaction tasks from which trained observers coded PD/AW. Another team of raters coded TD/AW during two early BSFT sessions. The main dependent variable was the number of drug-use days that adolescents reported in timeline follow-back interviews 7 to 12 months after family therapy began. Zero-inflated Poisson regression analyses supported the main hypothesis, showing that PD/AW and TD/AW interacted to predict adolescent drug use at follow-up. For adolescents in high PD/AW families, higher levels of TD/AW predicted significant increases in drug use at follow-up, whereas for low PD/AW families, TD/AW and follow-up drug use were unrelated. Results suggest that attending to parallel demand-withdraw processes in parent-adolescent and therapist-adolescent dyads may be useful in family therapy for substance-using adolescents. Rynes KN, Rohrbaugh MJ, Lebensohn-Chialvo F, Shoham V. Parallel Demand-Withdraw Processes in Family Therapy for Adolescent Drug Abuse. Psychol Addict Behav. 2013 Feb 25. [Epub ahead of print].

Differences between Men and Women in Condom Use, Attitudes, and Skills in Substance Abuse Treatment Seekers For substance abuse treatment-seekers engaging in high risk sexual behavior, their inconsistent condom use may be related to their condom use attitudes and skills. This study compared treatment-seeking male and female substance abusers in their reported barriers to condom use and condom use skills. Men and women (N=1,105) enrolled in two multi-site HIV risk reduction studies were administered the Condom Barriers Scale, Condom Use Skills, and an audio computer-assisted structured interview assessing sexual risk behavior. Men endorsed more barriers to condom use, especially on the Effects on Sexual Experience factor. For both men and women, stronger endorsement of barriers to condom use was associated with less use of condoms. However, the difference between condom users and non-users in endorsement of condom barriers in general is greater for men than women, especially for those who report having casual partners. Findings support the need to focus on gender-specific barriers to condom use in HIV/STI prevention interventions, especially risk behavior intervention techniques that address sexual experience with condoms. Results provide additional information about the treatment and prevention needs of treatment-seeking men and women. Calsyn DA, Peavy M, Wells EA, Campbell AN, Hatch-Maillette MA, Greenfield SF, Tross S. Differences between men and women in condom use, attitudes, and skills in substance abuse treatment seekers. Am J Addict. 2013 Mar; 22(2): 150-157.

INTRAMURAL RESEARCH

Synaptic Plasticity Section

Synaptic and Behavioral Profile Of Multiple Glutamatergic Inputs To The Nucleus Accumbens Excitatory afferents to the nucleus accumbens (NAc) are thought to facilitate reward seeking by encoding reward-associated cues. Selective activation of different glutamatergic inputs to the NAc can produce divergent physiological and behavioral responses, but mechanistic explanations for these pathway-specific effects are lacking. Here, IRP scientists compared the innervation patterns and synaptic properties of ventral hippocampus, basolateral amygdala, and prefrontal cortex input to the NAc. Ventral hippocampal input was found to be uniquely localized to the medial NAc shell, where it was predominant and selectively potentiated after cocaine exposure. In vivo, bidirectional optogenetic manipulations of this pathway attenuated and enhanced cocaine-induced locomotion. Challenging the idea that any of these inputs encode motivationally neutral information, activation of each discrete pathway reinforced instrumental behaviors. Finally, direct optical activation of medium spiny neurons proved to be capable of supporting self-stimulation, demonstrating that behavioral reinforcement is an explicit consequence of strong excitatory drive to the NAc. Britt JP, Benaliouad F, McDevitt RA, Stuber GD, Wise RA, Bonci A. Synaptic and behavioral profile of multiple glutamatergic inputs to the nucleus accumbens. Neuron 2013; 76(4): 790-803.

CRF Acts In The Midbrain To Attenuate Accumbens Dopamine Release To Rewards But Not Their Predictors Stressors affect dopamine-dependent behaviors such as motivation, although the underlying neurobiological mechanism is not well defined. IRP investigators report that corticotropin-releasing factor (CRF) acts in the ventral tegmental area (VTA) to reduce the motivation to work for food rewards. CRF in the VTA regulates dopamine output in a stimulus- and pathway-specific manner, offering a mechanism by which acute stress selectively regulates information transmission via the VTA to reprioritize motivated behavior. Wanat M J, Bonci A, Phillips PE CRF acts in the midbrain to attenuate accumbens dopamine release to rewards but not their predictors. Nat Neurosci. 2013: Epub ahead of print doi:10.1038/nn.3335

Rescuing Cocaine-Induced Prefrontal Cortex Hypoactivity Prevents Compulsive Cocaine Seeking Loss of control over harmful drug seeking is one of the most intractable aspects of addiction, as human substance abusers continue to pursue drugs despite incurring significant negative consequences. Human studies have suggested that deficits in prefrontal cortical function and consequential loss of inhibitory control could be crucial in promoting compulsive drug use. However, it remains unknown whether chronic drug use compromises cortical activity and, equally important, whether this deficit promotes compulsive cocaine seeking. Here the authors use a rat model of compulsive drug seeking in which cocaine seeking persists in a subgroup of rats despite delivery of noxious foot shocks. They show that prolonged cocaine self-administration decreases ex vivo intrinsic excitability of deeplayer pyramidal neurons in the prelimbic cortex, which was significantly more pronounced in compulsive drug-seeking animals. Furthermore, compensating for hypoactive prelimbic cortex neurons with in vivo optogenetic prelimbic cortex stimulation significantly prevented compulsive cocaine seeking, whereas optogenetic prelimbic cortex inhibition significantly increased compulsive cocaine seeking. These results show a marked reduction in prelimbic cortex excitability in compulsive cocaine-seeking rats, and that in vivo optogenetic prelimbic cortex stimulation decreased compulsive drug-seeking behaviours. Thus, targeted stimulation of the prefrontal cortex could serve as a promising therapy for treating

compulsive drug use. Chen BT, Yau HJ, Hatch C, Kusumoto-Yoshida I, Cho SL, Hopf FW, Bonci A. Rescuing cocaine-induced prefrontal cortex hypoactivity prevents compulsive cocaine seeking. Nature e-pub online 2013.

Dynamic Interaction Between Sigma-1 Receptor and Kv1.2 Shapes Neuronal and Behavioral Responses To Cocaine The sigma-1 receptor (Sig-1R), an endoplasmic reticulum (ER) chaperone protein, is an interorganelle signaling modulator that potentially plays a role in drug-seeking behaviors. However, the brain site of action and underlying cellular mechanisms remain unidentified. IRP researchers found that cocaine exposure triggers a Sig-1R-dependent upregulation of D-type K(+) current in the nucleus accumbens (NAc) that results in neuronal hypoactivity and thereby enhances behavioral cocaine response. Combining ex vivo and in vitro studies, the authors demonstrated that this neuroadaptation is caused by a persistent protein-protein association between Sig-1Rs and Kv1.2 channels, a phenomenon that is associated to a redistribution of both proteins from intracellular compartments to the plasma membrane. In conclusion, the dynamic Sig-1R-Kv1.2 complex represents a mechanism that shapes neuronal and behavioral response to cocaine. Functional consequences of Sig-1R binding to K(+) channels may have implications for other chronic diseases where maladaptive intrinsic plasticity and Sig-1Rs are engaged. Kourrich S, Hayashi T, Tsai SY, Harvey B, Su TP, Bonci A. Dynamic interaction between Sigma-1 receptor and Kv1.2 shapes neuronal and behavioral responses to cocaine. Cell 2013; 152(1-2): 236-247.

Integrative Neurobiology Section

Detection Of Receptor Heteromers Involving Dopamine Receptors By tThe Sequential BRET-FRET Technology Until very recently, dopamine receptors, like other G-protein-coupled receptors, were believed to function as individual units on the cell surface. Now it has been described by several groups including IRP scientists that dopamine receptors not only function as homomers but also form heteromers with other receptors at the membrane level. Bioluminescence and fluorescence resonance energy transfer (BRET and FRET) based techniques have been very useful to determine the interaction between two receptors, but to demonstrate the existence of higher-order complexes involving more than two molecules requires more sophisticated techniques. Combining BRET and FRET in the Sequential BRET-FRET (SRET) technique permits heteromers formed by three different proteins to be identified. In SRET experiments, the oxidation of a Renilla Luciferase substrate triggers acceptor excitation by BRET and subsequent energy transfer to a FRET acceptor. Using this methodology here the authors describe the heteromerization between adenosine A(2A), dopamine D(2), and cannabinoids CB(1) receptors in living cells. Navarro G, McCormick PJ, Mallol J, Lluís C, Franco R, Cortés A, Casadó V, Canela EI, Ferré S. Detection of receptor heteromers involving dopamine receptors by the sequential BRET-FRET technology. Methods Mol Biol. 2013; 964: 95-105.

Psychostimulant Pharmacological Profile Of Paraxanthine, the Main Metabolite Of Caffeine In Humans Caffeine induces locomotor activation by its ability to block adenosine receptors. Caffeine is metabolized to several methylxanthines, with paraxanthine being the main metabolite in humans. In this study the authors show that in rats paraxanthine has a stronger locomotor activating effect than caffeine or the two other main metabolites of caffeine, theophylline and theobromine. As previously described for caffeine, the locomotor activating doses of paraxanthine more efficiently counteract the locomotor depressant effects of an adenosine A(1) than an adenosine A(2A) receptor agonist. In drug discrimination experiments in rats trained to discriminate a maximal locomotor

activating dose of caffeine, paraxanthine, unlike theophylline, generalized poorly to caffeine suggesting the existence of additional mechanisms other than adenosine antagonism in the behavioral effects of paraxanthine. Pretreatment with the nitric oxide inhibitor N(G)-nitro-l-arginine methyl ester (l-NAME) reduced the locomotor activating effects of paraxanthine, but not caffeine. On the other hand, pretreatment with the selective cGMP-preferring phosphodiesterase PDE9 inhibitor BAY 73-6691, increased locomotor activity induced by caffeine, but not paraxanthine. Ex vivo experiments demonstrated that paraxanthine, but not caffeine, can induce cGMP accumulation in the rat striatum. Finally, in vivo microdialysis experiments showed that paraxanthine, but not caffeine, significantly increases extracellular levels of dopamine in the dorsolateral striatum, which was blocked by l-NAME. These findings indicate that inhibition of cGMP-preferring PDE is involved in the locomotor activating effects of the acute administration of paraxanthine. The present results demonstrate a unique psychostimulant profile of paraxanthine, which might contribute to the reinforcing effects of caffeine in humans. Orrú M, Guitart X, Karcz-Kubicha M, Solinas M, Justinova Z, Barodia SK, Zanoveli J, Cortes A, Lluis C, Casado V, Moeller FG, Ferré S. Pychostimulant pharmacological profile of paraxanthine, the main metabolite of caffeine in humans. Neuropharmacology. 2013 Apr; 67: 476-484.

Cardiovascular and Subjective Effects Of the Novel Adenosine A(2A) Receptor Antagonist SYN115 In Cocaine Dependent Individuals A(2A) receptor antagonists have been proposed as therapeutic tools for dopaminergically-relevant diseases, including Parkinson's disease and substance dependence. The acute subjective and cardiovascular effects of a novel, selective adenosine A(2A) receptor antagonist (SYN115) were examined. Across an 8-hour experimental testing day, 22 non-treatment seeking cocaine-dependent subjects received either placebo capsules (PO) at both the AM and PM dosing times (Plc/Plc, N = 9), or placebo in the AM and 100 mg SYN115 in the PM (Plc/SYN115, N =13). Cardiovascular measures (HR, BP) were obtained across the test day, and subjective effects (ARCI, VAS) were obtained once before and once after the AM and PM doses (four time points total). There were no between-group effects on cardiovascular function, however subjective effects consistent with stimulation were observed on the VAS scales in the SYN115 group. In cocaine-dependent subjects, SYN115 may produce stimulant-like effects through a unique mechanism of action. Due to known monoamine dysfunction related to chronic cocaine use, these effects may be specific to this population relative to healthy control or other patient populations. Lane S, Green C, Steinberg J, Ma L, Schmitz J, Rathnayaka N, Bandak S, Ferre S, Moeller F. Cardiovascular and subjective effects of the novel adenosine A(2A) receptor antagonist SYN115 in cocaine dependent individuals. J Addict Res Ther. 2012 Mar 28;S1.

Circadian-Related Heteromerization Of Adrenergic and Dopamine D Receptors Modulates Melatonin Synthesis And Release In The Pineal Gland The role of the pineal gland is to translate the rhythmic cycles of night and day encoded by the retina into hormonal signals that are transmitted to the rest of the neuronal system in the form of serotonin and melatonin synthesis and release. Here the authors describe that the production of both melatonin and serotonin by the pineal gland is regulated by a circadian-related heteromerization of adrenergic and dopamine D_4 receptors. Through $\alpha(_1B)$-D_4 and β_1-D_4 receptor heteromers dopamine inhibits adrenergic receptor signaling and blocks the synthesis of melatonin induced by adrenergic receptor ligands. This inhibition was not observed at hours of the day when D_4 was not expressed. These data provide a new perspective on dopamine function and constitute the first example of a circadian-controlled receptor heteromer. The unanticipated heteromerization between adrenergic and dopamine D_4 receptors provides a feedback mechanism for the neuronal hormone system in the form of dopamine to control circadian

inputs. Circadian-related heteromerization of adrenergic and dopamine d receptors modulates melatonin synthesis and release in the pineal gland. González S, Moreno-Delgado D, Moreno E, Pérez-Capote K, Franco R, Mallol J, Cortés A, Casadó V, Lluís C, Ortiz J, Ferré S, Canela E, McCormick PJ. PLoS Biol. 2012; 10(6); e1001347.

Increased Orbitofrontal Brain Activation After Administration Of A Selective Adenosine A(2A) Antagonist In Cocaine Dependent Subjects Positron Emission Tomography imaging studies provide evidence of reduced dopamine function in cocaine dependent subjects in the striatum, which is correlated with prefrontal cortical glucose metabolism, particularly in the orbitofrontal cortex. However, whether enhancement of dopamine in the striatum in cocaine dependent subjects would be associated with changes in prefrontal cortical brain activation is unknown. One novel class of medications that enhance dopamine function via heteromer formation with dopamine receptors in the striatum is the selective adenosine A(2A) receptor antagonists. This study sought to determine the effects administration of the selective adenosine A(2A) receptor antagonist SYN115 on brain function in cocaine dependent subjects. Methodology/Principle Findings: Twelve cocaine dependent subjects underwent two fMRI scans (one after a dose of placebo and one after a dose of 100 mg of SYN115) while performing a working memory task with three levels of difficulty (3, 5, and 7 digits). fMRI results showed that for 7-digit working memory activation there was significantly greater activation from SYN115 compared to placebo in portions of left (L) lateral orbitofrontal cortex, L insula, and L superior and middle temporal pole. Conclusion/Significance: These findings are consistent with enhanced dopamine function in the striatum in cocaine dependent subjects via blockade of adenosine A(2A) receptors producing increased brain activation in the orbitofrontal cortex and other cortical regions. This suggests that at least some of the changes in brain activation in prefrontal cortical regions in cocaine dependent subjects may be related to altered striatal dopamine function, and that enhancement of dopamine function via adenosine A(2A) receptor blockade could be explored further for amelioration of neurobehavioral deficits associated with chronic cocaine use. Moeller FG, Steinberg JL, Lane SD, Kjome KL, Ma L, Ferre S, Schmitz JM, Green CE, Bandak SI, Renshaw PF, Kramer LA, Narayana PA. Increased orbitofrontal brain activation after administration of a selective adenosine A(2A) antagonist in cocaine dependent subjects. Front Psychiatry. 2012; 3: 44.

Evidence That Sleep Deprivation Downregulates Dopamine D2R In Ventral Striatum In the Human Brain Dopamine D2 receptors are involved with wakefulness, but their role in the decreased alertness associated with sleep deprivation is unclear. IRP scientists had shown that sleep deprivation reduced dopamine D2/D3 receptor availability (measured with PET and [(11)C]raclopride in controls) in striatum, but could not determine whether this reflected dopamine increases ([(11)C]raclopride competes with dopamine for D2/D3 receptor binding) or receptor down-regulation. To clarify this, the authors compared the dopamine increases induced by methylphenidate (a drug that increases dopamine by blocking dopamine transporters) during sleep deprivation versus rested sleep, with the assumption that methylphenidate's effects would be greater if, indeed, dopamine release was increased during sleep deprivation. They scanned 20 controls with [(11)C]raclopride after rested sleep and after 1 night of sleep deprivation; both after placebo and after methylphenidate. The authors corroborated a decrease in D2/D3 receptor availability in the ventral striatum with sleep deprivation (compared with rested sleep) that was associated with reduced alertness and increased sleepiness. However, the dopamine increases induced by methylphenidate (measured as decreases in D2/D3 receptor availability compared with placebo) did not differ between rested sleep and sleep deprivation, and were associated with the increased alertness and reduced sleepiness when methylphenidate was administered after sleep deprivation.

Similar findings were obtained by microdialysis in rodents subjected to 1 night of paradoxical sleep deprivation. These findings are consistent with a downregulation of D2/D3 receptors in ventral striatum with sleep deprivation that may contribute to the associated decreased wakefulness and also corroborate an enhancement of D2 receptor signaling in the arousing effects of methylphenidate in humans. Volkow ND, Tomasi D, Wang GJ, Telang F, Fowler JS, Logan J, Benveniste H, Kim R, Thanos PK, Ferré S. Evidence that sleep deprivation downregulates dopamine D2R in ventral striatum in the human brain. J Neurosci. 2012 May 9; 32(19): 6711-6717.

Optogenetics and Transgenic Technology Core (OTTC) and Glia-Neuron Interactions (GNI) Lab

Mesencephalic Astrocyte-Derived Neurotrophic Factor (MANF) Secretion and Cell Surface Binding Are Modulated By KDEL Receptors Mesencephalic astrocyte-derived neurotrophic factor (MANF) is an endoplasmic reticulum (ER) stress-responsive protein with neuroprotective effects in animal models of neurodegeneration, but the underlying mechanism is not understood. IRP investigators constructed a set of lentiviral vectors that contain or lack the highly conserved final four amino acids of MANF ("RTDL"), which resemble the canonical ER retention signal ("KDEL"), to study MANF regulation in neuroblastoma cells and rat primary cortical neurons. The RTDL sequence was required for both ER retention and secretory response to ER stress. Overexpression of KDEL receptor paralogs (KDELRs) differentially reduced MANF secretion but had no effect on MANF lacking RTDL. MANF binding to the plasma membrane also required the RTDL sequence and was inhibited with a peptide known to interact with KDELRs, suggesting MANF binds KDELRs at the surface. The authors detected surface localization of FLAG-tagged KDELRs, with levels increasing following ER stress. This study provides new insight into the regulation of MANF trafficking and has implications for other secreted proteins containing a KDEL-like retention signal. Henderson MJ, Richie CT, Airavaara M, Wang Y, Harvey BK. J Biol Chem. 2013 Feb 8; 288(6): 4209-4225. doi: 10.1074/jbc.M112.400648. Epub 2012 Dec 19. PMID: 23255601,

Patent

THERAPEUTIC POLYPEPTIDES AND METHODS OF THEIR USE
Disclosed in the patent is the unexpected discovery that the C-terminal four amino acids of MANF (RTDL), as well as other related sequences, have therapeutic utility for inhibition of ER stress, and therefore can be used for the treatment and inhibition of ER-stress related disorders. Additionally disclosed is the surprising finding that a polypeptide including an N-terminal signal peptide and the C-terminal four amino acids of MANF (RTDL) or other related sequences, can be used as a sensor of ER stress in a cell. Inventors: Brandon K. Harvey, Mark J. Henderson, Mikko T. Airavaara and Christopher Richie.

Psychobiology Section, Molecular Targets and Medications Discovery Branch

Self-Administration Of Cocaine Induces Dopamine-Independent Self-Administration Of Sigma Agonists Sigma$_1$ receptors (σ_1Rs) are intracellularly-mobile chaperone proteins implicated in several disease processes, as well as psychiatric disorders and substance abuse. Here the authors report that although selective σ_1R agonists (PRE-084, (+)-pentazocine) lacked reinforcing effects in

drug-naive rats; over the course of 28 experimental sessions, which was more than sufficient for acquisition of cocaine self-administration, responding was not maintained by either σ_1R agonist. In contrast, after subjects self-administered cocaine σ_1R agonists were readily self-administered. The induced reinforcing effects were long lasting; a response for which subjects had no history of reinforcement was newly conditioned with both σ_1R agonists, extinguished when injections were discontinued, and reconditioned when σ_1R agonists again followed responses. Experience with food reinforcement was ineffective as an inducer of σ_1R agonist reinforcement. While a variety of dopamine-receptor antagonists blocked cocaine self-administration, consistent with its dopaminergic mechanism, PRE-084 self-administration was entirely insensitive to these drugs. Conversely, the σR antagonist, BD1063, blocked PRE-084 self-administration but was inactive against cocaine. In microdialysis studies i.v. PRE-084 did not significantly stimulate dopamine at doses that were self-administered in rats either with or without a cocaine self-administration experience. The results indicate that cocaine experience induces reinforcing effects of previously inactive σ_1R agonists, and that the mechanism underlying these reinforcing effects is dopamine-independent. It is further suggested that induced σ_1R mechanisms may play an essential role in treatment-resistant stimulant abuse, suggesting new approaches for the development of effective medications for stimulant abuse. Hiranita, T, Mereu, M, Soto, PL, Tanda, G, Katz, JL. Self-administration of cocaine induces dopamine-independent self-administration of sigma agonists. Neuropsychopharmacology 2013; 38: 605–615.

Electrophysiology Research Section, Cellular Neurobiology Research Branch

Powerful Cocaine-Like Actions Of 3,4-Methylenedioxypyrovalerone (MDPV), A Principal Constituent Of Psychoactive 'Bath Salts' Products The abuse of psychoactive 'bath salts' containing cathinones such as 3,4-methylenedioxypyrovalerone (MDPV) is a growing public health concern, yet little is known about their pharmacology. Here, IRP researchers evaluated the effects of MDPV and related drugs using molecular, cellular, and whole-animal methods. In vitro transporter assays were performed in rat brain synaptosomes and in cells expressing human transporters, while clearance of endogenous dopamine was measured by fast-scan cyclic voltammetry in mouse striatal slices. Assessments of in vivo neurochemistry, locomotor activity, and cardiovascular parameters were carried out in rats. The authors found that MDPV blocks uptake of [(3)H]dopamine (IC(50)=4.1nM) and [(3)H]norepinephrine (IC(50)=26 nM) with high potency but has weak effects on uptake of [(3)H]serotonin (IC(50)=3349nM). In contrast to other psychoactive cathinones (eg, mephedrone), MDPV is not a transporter substrate. The clearance of endogenous dopamine is inhibited by MDPV and cocaine in a similar manner, but MDPV displays greater potency and efficacy. Consistent with in vitro findings, MDPV (0.1-0.3mg/kg, intravenous) increases extracellular concentrations of dopamine in the nucleus accumbens. Additionally, MDPV (0.1-3.0mg/kg, subcutaneous) is at least 10 times more potent than cocaine at producing locomotor activation, tachycardia, and hypertension in rats. These data show that MDPV is a monoamine transporter blocker with increased potency and selectivity for catecholamines when compared with cocaine. The robust stimulation of dopamine transmission by MDPV predicts serious potential for abuse and may provide a mechanism to explain the adverse effects observed in humans taking high doses of 'bath salts' preparations. Baumann MH, Partilla JS, Lehner KR, Thorndike EB, Hoffman AF, Holy M, Rothman RB, Goldberg SR, Lupica CR, Sitte HH, Brandt SD, Tella SR, Cozzi NV, Schindler CW. Powerful cocaine-like actions of 3,4-Methylenedioxypyrovalerone (MDPV), a principal constituent of psychoactive 'bath salts' products.Neuropsychopharmacology. 2013 Mar; 38(4): 552-562. doi: 10.1038/npp.2012.204. Epub 2012 Oct 17. PMID: 23072836

Synaptic Targets Of Δ^9-Tetrahydrocannabinol In The Central Nervous System The availability of potent synthetic agonists for cannabinoid receptors has facilitated our understanding of cannabinoid actions on synaptic transmission in the central nervous system. Moreover, the ability of these compounds to inhibit neurotransmitter release at many central synapses is thought to underlie most of the behavioral effects of cannabinoid agonists. However, despite the widespread use and misuse of marijuana, and recognition of its potential adverse psychological effects in humans, comparatively few studies have examined the actions of its primary psychoactive constituent, Δ(9)-tetrahydrocannabinol (THC), at well-defined synaptic pathways. Here the authors examine the recent literature describing the effects of acute and repeated THC exposure on synaptic function in several brain regions and explore the importance of these neurobiological actions of THC in drug addiction. Hoffman A, Lupica CR. Synaptic targets of Δ^9-tetrahydrocannabinol in the central nervous system.Cold Spring Harb Perspect Med. 2012 Dec 3. doi:pii: cshperspect. a012237v1. 10.1101/cshperspect.a012237. [Epub ahead of print].

Neuroimaging Research Branch

Insular and Anterior Cingulate Circuits In Smokers With Schizophrenia Schizophrenia (SZ) is associated with high rates of smoking. IRP scientists previously found that resting state functional connectivity (rsFC) between the dorsal anterior cingulate (dACC) and striatum is independently associated with nicotine addiction and psychiatric illness. Since the insula is implicated in nicotine dependence, they hypothesized that SZ smokers will have greater dysfunction in smoking-related insular and dACC circuits than normal control smokers (NC) independent of smoking severity, consistent with an inherent disease-related weakening of smoking-related circuits. Nicotine challenge was used to demonstrate that decreased rsFC in identified circuits reflects addiction trait and is not affected by pharmacological state. Twenty-four NC smokers and 20 smokers with SZ matched on nicotine addiction severity participated in a resting state fMRI study and were scanned during two separate sessions while receiving a placebo or nicotine patch, in a randomized, cross-over design. Using individualized, anatomically defined anterior and posterior insula and dACC as regions of interest (ROI), whole brain rsFC was performed using each ROI as a seed. Significant negative correlations between smoking severity and rsFC between insula, dACC and striatum were found for both groups. Furthermore, smokers with SZ demonstrated additive reductions in circuit strength between the dACC and insula compared to NC smokers independent of smoking severity. Nicotine challenge did not significantly alter rsFC in insula-dACC-striatal circuits. Reduced rsFC strength between the insula, dACC and striatum is associated with nicotine addiction severity in both non-psychiatrically ill and in SZ smokers. Decreased insula-dACC rsFC may index overlapping circuitry associated with smoking and SZ. Moran, LV, Sampath, H, Stein, EA, Hong, LE. Insula and anterior cingulate circuits in smokers with schizophrenia. Schizophrenia Research 2012; 142: 223-229.

The Roles Of Reward, Default, and Executive Control Networks In Set-Shifting Impairments In Schizophrenia Patients with schizophrenia (SZ) show deficits on tasks of rapid reinforcement learning, like probabilistic reversal learning (PRL), but the neural bases for those impairments are not known. Recent evidence of relatively intact sensitivity to negative outcomes in the ventral striatum (VS) in many SZ patients suggests that PRL deficits may be largely attributable to processes downstream from feedback processing, involving both the activation of executive control task regions and deactivation of default mode network (DMN) components. IRP investigators analyzed data from 29 chronic SZ patients and 21 matched normal controls (NCs) performing a

PRL task in an MRI scanner. Subjects were presented with eight pairs of fractal stimuli, for 50 trials each. For each pair, subjects learned to choose the more frequently-rewarded (better) stimulus. Each time a criterion was reached, the better stimulus became the worse one, and the worse became the better. Responses to feedback events were assessed through whole-brain and regions-of-interest (ROI) analyses in DMN. The authors also assessed correlations between BOLD signal contrasts and clinical measures in SZs. Relative to NCs, SZ patients showed comparable deactivation of VS in response to negative feedback, but reduced deactivation of DMN components including medial prefrontal cortex (mPFC). The magnitudes of patients' punishment-evoked deactivations in VS and ventromedial PFC correlated significantly with clinical ratings for avolition/anhedonia. These findings suggest that schizophrenia is associated with a reduced ability to deactivate components of default mode networks, following the presentation of informative feedback and that motivational deficits in SZ relate closely to feedback-evoked activity in reward circuit components. These results also confirm a role for ventrolateral and dorsomedial PFC in the execution of response-set shifts. Waltz JA, Kasanova, Z, Ross TJ, Salmeron BJ, McMahon, RP, Gold JM and Stein EA. The roles of reward, default, and executive control networks in set-shifting impairments in schizophrenia. PLoS ONE 2013; 8(2): e57257. doi:10.1371/journal.pone.0057257.

Prefrontal White Matter Impairment In Substance Users Depends Upon the Catechol-O-Methyl Transferase (COMT) Val158met Polymorphism Individuals addicted to most chemical substances present with hypoactive dopaminergic systems as well as altered prefrontal white matter structure. Prefrontal dopaminergic tone is under genetic control and is influenced by and modulates descending cortico-striatal glutamatergic pathways that in turn, regulate striatal dopamine release. The catechol-O methyltransferase (COMT) gene contains an evolutionarily recent and common functional variant at codon 108/158 (rs4680) that plays an important role in modulating prefrontal dopaminergic tone. To determine if the COMT val158met genotype influences white matter integrity (i.e., fractional anisotropy (FA)) in substance users, 126 healthy controls and 146 substance users underwent genotyping and magnetic resonance imaging. A general linear model with two between subjects factors (COMT genotype and addiction status) was performed using whole brain diffusion tensor imaging (DTI) to assess FA. A significant Genotype x Drug Use status interaction was found in the left prefrontal cortex. Post-hoc analysis showed reduced prefrontal FA only in Met/Met homozygotes who were also drug users. These data suggest that Met/Met homozygous individuals, in the context of addiction, have increased susceptibility to white matter structural alterations, which might contribute to previously identified structural and functional prefrontal cortical deficits in addiction. Zhang, X, Lee, MR, Salmeron, BJ, Stein, DL, Hong, LE, Geng, X, Ross, TJ, Wang, Y, Hodgkinson, C, Shen, P-H, Yang, Y, Goldman, D, Stein, EA. Prefrontal white matter impairment in substance users depends upon the catechol-o-methyl transferase (COMT) val158met polymorphism. NeuroImage 2013; 69: 62-69.

Acute Nicotine Differentially Impacts Anticipatory Valence- And Magnitude-Related Striatal Activity Dopaminergic activity plays a role in mediating the rewarding aspects of abused drugs, including nicotine. Nicotine modulates the reinforcing properties of other motivational stimuli, yet the mechanisms of this interaction are poorly understood. This study aimed to ascertain the impact of nicotine exposure on neuronal activity associated with reinforcing outcomes in dependent smokers. Smokers and control subjects underwent functional imaging during performance of a monetary incentive delay task. Using a randomized, counterbalanced design, smokers completed scanning after placement of a nicotine or placebo patch; nonsmokers were scanned twice without nicotine manipulation. In regions along dopaminergic pathway trajectories, we considered event-related activity for valence (reward/gain vs. punishment/loss), magnitude (small, medium, large),

and outcome (successful vs. unsuccessful). Both nicotine and placebo patch conditions were associated with reduced activity in regions supporting anticipatory valence, including ventral striatum. In contrast, relative to controls, acute nicotine increased activity in dorsal striatum for anticipated magnitude. Across conditions, anticipatory valence-related activity in the striatum was negatively associated with plasma nicotine concentration, whereas the number of cigarettes daily correlated negatively with loss anticipation activity in the medial prefrontal cortex only during abstinence. These data suggest a partial dissociation in the state- and trait-specific effects of smoking and nicotine exposure on magnitude- and valence-dependent anticipatory activity within discrete reward processing brain regions. Such variability may help explain, in part, nicotine's impact on the reinforcing properties of nondrug stimuli and speak to the continued motivation to smoke and cessation difficulty. Rose, EJ, Ross, TJ, Salmeron, BJ, Lee, M, Shakleya, DM, Huestis, MA, Stein, EA. Acute nicotine differentially impacts anticipatory valence- and magnitude-related striatal activity. Biological Psychiatry 2013; 73: 280-288.

Neuropsychopharmacology Section, Chemical Biology Research Branch

Cocaine-Taking and Cocaine-Seeking Behaviors In Rats Remain Stable After Systemic Administration Of GYKI 52466: A Non-Competitive AMPA Receptor Antagonist Given the posited role of enhanced AMPA-mediated synaptic transmission in relapse to drug seeking, IRP scientists investigated whether systemic administration of the AMPA receptor antagonist GYKI 52466 inhibits cocaine-taking and cocaine-seeking behavior in rats. Rats were trained to self-administer cocaine until stable self-administration was achieved. Effects of GYKI 52466 (1, 3, or 10mg/kg, i.v.) on cocaine self-administration were assessed. Animals were allowed to re-establish stable cocaine self-administration and were then behaviorally extinguished from drug taking. The effects of GYKI 52466 (3, 10mg/kg, i.v.) on cocaine-induced reinstatement of drug-seeking behavior were assessed. The authors found that GYKI 52466 failed to inhibit cocaine-taking and cocaine-seeking in both the self-administration and reinstatement paradigms. They suggest that although AMPA receptors may be involved in cocaine reward and addiction, the AMPA receptor antagonist GYKI 52466 has low therapeutic potential for cocaine addiction treatment. Srivastava R, Xi Z-X, Gardner EL. Cocaine-taking and cocaine-seeking behaviors in rats remain stable after systemic administration of GYKI 52466: a non-competitive AMPA receptor antagonist. Neurosci Lett. 2012; 508(2): 106-109.

Blockade Of Dopamine D_3 Receptors In the Nucleus Accumbens and Central Amygdala Inhibits Incubation Of Cocaine Craving In Rats Cue-induced drug seeking progressively increases over time of withdrawal from drug self-administration in rats, a phenomenon called "incubation of craving." The underlying mechanisms have been linked to increased expression of brain-derived neurotrophic factor and GluR2-lacking AMPA receptors in the mesolimbic dopamine (DA) system and also to increased extracellular signal-regulated kinase activation in the central amygdala (CeA). However, it remains unclear whether any DA mechanism is also involved in incubation of craving. Recent research demonstrates that cue-induced cocaine seeking appears to parallel increased DA D3, but not D1 or D2, receptor expression in the nucleus accumbens (NAc) of rats over time of withdrawal, suggesting possible involvement of D3 receptors (D3Rs) in incubation of cocaine craving. Here, the authors report that systemic or local administration of SB-277011A, a highly selective D3R antagonist, into the NAc (core and shell) or the CeA, but not the dorsal striatum or basolateral amygdala, significantly inhibits expression of incubation of cocaine craving in rats after 2-30 days of withdrawal from previous cocaine self-administration but had no effect on sucrose-seeking behavior in rats after 10-30 days of withdrawal. These data suggest that

DA D3Rs in both the NAc and the CeA play an important role in incubation of cocaine craving in rats and support the potential utility of D3R antagonists in the treatment of cocaine addiction. Xi Z-X, Li X, Li J, Peng X-Q, Song R, Gaál J, Gardner EL. Blockade of dopamine D_3 receptors in the nucleus accumbens and central amygdala inhibits incubation of cocaine craving in rats. Addict Biol. 2012, Epub ahead of print 23 Aug 2012.

Increased Vulnerability To Cocaine In Mice Lacking Dopamine D3 Receptors Neuroimaging studies using positron emission tomography suggest that reduced dopamine D2 receptor availability in the neostriatum is associated with increased vulnerability to drug addiction in humans and experimental animals. The role of D3 receptors (D3Rs) in the neurobiology of addiction remains unclear, however. Here the authors report that D3R KO ($D3^{-/-}$) mice display enhanced cocaine self-administration and enhanced motivation for cocaine-taking and cocaine-seeking behavior. This increased vulnerability to cocaine is accompanied by decreased dopamine response to cocaine secondary to increased basal levels of extracellular dopamine in the nucleus accumbens, suggesting a compensatory response to decreased cocaine reward in $D3^{-/-}$ mice. In addition, $D3^{-/-}$ mice also display up-regulation of dopamine transporters in the striatum, suggesting a neuroadaptative attempt to normalize elevated basal extracellular dopamine. These findings suggest that D3R deletion increases vulnerability to cocaine, and that reduced D3R availability in the brain may constitute a risk factor for the development of cocaine addiction. Song R, Zhang H-Y, Li X, Bi G-H, Gardner EL, Xi Z-X. Increased vulnerability to cocaine in mice lacking dopamine D3 receptors. Proc Natl Acad Sci USA. 2012; 109(43): 17675-17680.

The Selective D3 Receptor Antagonist SB-277011A Attenuates Morphine-Triggered Reactivation Of Expression Of Cocaine-Induced Conditioned Place Preference IRP scientists examined the effect of acute administration of the selective D3 receptor antagonist SB-277011A on morphine-triggered reactivation of cocaine-induced conditioned place preference (CPP) in adult male Sprague-Dawley rats. Repeated pairing of animals with 15 mg/kg i.p. of cocaine HCl or vehicle to cue-specific CPP chambers produced a significant CPP response compared to animals paired only with vehicle in both chambers. Expression of the CPP response to cocaine was then extinguished by repeatedly giving the animals vehicle injections in the cocaine-paired chambers. The magnitude of the CPP response after extinction was not significantly different from that of animals paired only with vehicle. Expression of the extinguished CPP response was reactivated by acute administration of 5 mg/kg i.p. of morphine but not by vehicle. Acute administration of 6 or 12 mg/kg i.p. (but not 3 mg/kg) of SB-277011A significantly attenuated morphine-triggered reactivation of the cocaine-induced CPP. SB-277011A itself (12 mg/kg i.p.) did not reactivate the extinguished CPP response. Overall, SB-277011A decreases the incentive motivational actions of morphine. The present findings suggest that central D3 dopamine receptors are involved in relapse to cocaine-seeking behavior, that a final common neural mechanism exists to mediate the incentive motivational effects of psychostimulants and opiates, and that selective dopamine D3 receptor antagonists constitute promising compounds for treating addiction. Rice OV, Heidbreder CA, Gardner EL, Schonhar CD, Ashby CR Jr. The selective D3 receptor antagonist SB-277011A attenuates morphine-triggered reactivation of expression of cocaine-induced conditioned place preference. Synapse. 2013, Epub ahead of print 13 Feb 2013.

Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch

Inhibition Of FAAH and Activation Of PPAR: New Approaches To the Treatment Of Cognitive Dysfunction and Drug Addiction Enhancing the effects of endogenously-released cannabinoid ligands in the brain might provide therapeutic effects more safely and effectively than administering drugs that act directly at the cannabinoid receptor. Inhibitors of fatty acid amide hydrolase (FAAH) prevent the breakdown of endogenous ligands for cannabinoid receptors and peroxisome proliferator-activated receptors (PPAR), prolonging and enhancing the effects of these ligands when they are naturally released. This review considers recent research on the effects of FAAH inhibitors and PPAR activators in animal models of addiction and cognition (specifically learning and memory). These studies show that FAAH inhibitors can produce potentially therapeutic effects, some through cannabinoid receptors and some through PPAR. These effects include enhancing certain forms of learning, counteracting the rewarding effects of nicotine and alcohol, relieving symptoms of withdrawal from cannabis and other drugs, and protecting against relapse-like reinstatement of drug self-administration. Since FAAH inhibition might have a wide range of therapeutic actions but might also share some of the adverse effects of cannabis, it is noteworthy that at least one FAAH-inhibiting drug (URB597) has been found to have potentially beneficial effects but no indication of liability for abuse or dependence. Although these areas of research are new, the preliminary evidence indicates that they might lead to improved therapeutic interventions and a better understanding of the brain mechanisms underlying addiction and memory. Panlilio LV, Justinova Z, Goldberg SR. Inhibition of FAAH and activation of PPAR: New approaches to the treatment of cognitive dysfunction and drug addiction. Pharmacol. Ther. 2013; 138(1): 84-102.

Prior Exposure To THC Increases the Addictive Effects Of Nicotine In Rats Although it is more common for drug abuse to progress from tobacco to cannabis, in many cases cannabis use develops before tobacco use. Epidemiological evidence indicates that prior cannabis use increases the likelihood of becoming dependent on tobacco. To determine whether this effect might be due to cannabis exposure per se, in addition to any genetic, social, or environmental factors that might contribute, IRP researchers extended their series of studies on 'gateway drug' effects in animal models of drug abuse. Rats were exposed to THC, the main psychoactive constituent of cannabis, for 3 days (two intraperitoneal injections/day). Then, starting 1 week later, they were allowed to self-administer nicotine intravenously. THC exposure increased the likelihood of acquiring the nicotine self-administration response from 65% in vehicle-exposed rats to 94% in THC-exposed rats. When the price of nicotine was manipulated by increasing the response requirement, THC-exposed rats maintained higher levels of intake than vehicle-exposed rats, indicating that THC exposure increased the value of nicotine reward. These results contrast sharply with the authors' earlier findings that prior THC exposure did not increase the likelihood of rats acquiring either heroin or cocaine self-administration, nor did it increase the reward value of these drugs. The findings obtained here suggest that a history of cannabis exposure might have lasting effects that increase the risk of becoming addicted to nicotine. Panlilio LV, Zanettini C, Barnes C, Solinas M, Goldberg SR. Prior exposure to THC increases the addictive effects of nicotine in rats. Neuropsychopharmacology advance online publication, 6 February 2013; doi:10.1038/ npp.2013.16.

AM404 Attenuates Reinstatement Of Nicotine Seeking Induced By Nicotine-Associated Cues and Nicotine Priming But Does Not Affect Nicotine- and Food-Taking Multiple studies suggest a pivotal role of the endocannabinoid system in the regulation of the reinforcing effects of various substances of abuse. Different approaches have been used to modulate endocannabinoid neurotransmission including the use of endogenous cannabinoid anandamide reuptake inhibitors. Previously, the effects of one of them, N-(4-hydroxyphenyl)-arachidonamide (AM404), have been explored in rodents trained to self-administer ethanol and heroin, producing some promising results. Moreover, AM404 attenuated the development and reinstatement of nicotine-induced conditioned place preference (CPP). In this study, IRP scientists used the nicotine intravenous self-administration procedure to assess the effects of intraperitoneal administration of 0, 1, 3 and 10 mg/kg AM404 on nicotine-taking and food-taking behaviors under fixed-ratio and progressive-ratio schedules of reinforcement, as well as on reinstatement of nicotine-seeking induced by nicotine priming and by presentation of nicotine-associated cues. The ability of AM404 to produce place preference was also evaluated. AM404 did not produce CPP and did not modify nicotine-taking and food-taking behaviors. In contrast, AM404 dose-dependently attenuated reinstatement of nicotine-seeking behavior induced by both nicotine-associated cues and nicotine priming. The results indicate that AM404 could be a potential promising therapeutic option for the prevention of relapse to nicotine-seeking in abstinent smokers. Gamaleddin I, Guranda M, Scherma M, Fratta W, Makriyannis A, Vadivel SK, Goldberg SR, Le Foll B. AM404 attenuates reinstatement of nicotine seeking induced by nicotine-associated cues and nicotine priming but does not affect nicotine- and food-taking. J Psychopharmacol 2013, epub Feb 20, 2013.

Structural Biology Unit, Integrative Neuroscience, Integrative Neuroscience Branch

How Adenylate Cyclase Choreographs The Pas De Deux Of The Receptors Heteromerization Dance The authors' work on D2R/D4R heteromer formation with Adenosine A2A, suggests that receptors heteromer formation, mainly involves linear motifs found in disordered regions of receptors' proteins. Local disorder imparts plasticity to linear motifs (LMs). Many molecular recognition of proteins occur between short linear segments, known as LMs. Interaction of short continuous epitopes are not constrained by sequence and have the advantage of resulting in interactions with micromolar affinities which suites transient, reversible complexes such as receptor heteromers. Electrostatic Interactions between epitopes of the GPCR involved, is the Key step in driving heteromer formation forward. The first step in heteromerization, involves phosphorylating the Ser/Thr in an epitope containing a casein kinase 1/2 (*CK1/2)-consensus site.* The authors' data suggest that dopaminergic neurotransmission, through cAMP dependent PKA slows down heteromerization. The negative charge, acquired by phosphorylation of a Ser/Thr in a PKA consensus site in the Arg rich epitope, affects the activity of the receptors involved in heteromerization by causing allosteric conformational changes, due to the repulsive effect generated by the negatively charged phosphate. In addition to modulating heteromerization, it affects the stability of the heteromers' interactions and their binding affinity. So here we have an instance where *phosphorylation is not just an on/off switch*, instead by weakening the noncovalent bond, heteromerization acts like a rheostat that controls the stability of the heteromer through activation or inhibition of adenylate cyclase (AC) by the neurotransmitter Dopamine depending on which Dopamine receptor it docks at. The authors previously demonstrated that phosphorylation is a major regulatory mechanism in receptor heteromerization, and that the region's environment, i.e. amino acid composition, sequence complexity, hydrophobicity, charge and other sequence attributes of regions adjacent to phosphorylation sites, are very similar to those of intrinsically disordered protein

motifs. This provides strong support for the hypothesis that protein phosphorylation occurs predominantly within intrinsically disordered protein regions. Conformational changes upon phosphorylation often affect protein function. The high disorder and secondary structure patterns detected in all receptors examined, suggest the presence of molecular recognition elements (MoREs) that may mediate phosphorylation-regulated intra- and inter-domain interactions. Dunker and Fuxreiter proposed that proteins have such structural elements or features that mediate the binding events of disordered regions and that this element consists of a short linear region (LM) that undergoes coupled binding and folding within a longer region of disorder and called these features "molecular recognition elements" (MoREs). The authors believe that positively and negatively charged epitopes in receptors are the molecular recognition elements involved in heteromerization. The electrostatic interaction between these charged epitopes is the first and essential step that drives receptors to form heteromers; addition of a phosphate next to the Arg rich motif decreases the positive charge of the epitope, resulting in the weakening of the electrostatic interaction that leads to heteromer formation. Our data suggests that phosphorylation of the positive epitope decreases heteromerization by 40-50%. It also suggests that ligands (Dopamine and Adenosine) have a say in heteromerization and can alter the stability of heteromers, once they are formed. In other words, the phosphorylation state sets the "gain" of the system, and determines whether Dopamine or Adenosine will be effective or not in activating a receptor, if this receptor is involved in formation of a heteromer. Hence when Dopamine is around D2R/ D4R are in charge, while when Adenosine is, A2AR has the upper hand, which explains why the pharmaceutical properties of compounds are altered when receptors form heteromers or a mosaic. Woods AS, Jackson SN How adenylate cyclase choreographs the pas de deux of the Receptors heteromerization dance. Neuroscience. E-pub February 19, 2013.

Gangliosides and Ceramides Change In A Mouse Model Of Blast Induced Traumatic Brain Injury Explosive detonations generate atmospheric pressure changes that produce non-penetrating blast induced "mild" traumatic brain injury (bTBI). The structural basis for mild bTBI has been extremely controversial. The present study applies matrix-assisted laser desorption/ionization (MALDI) mass spectrometry imaging to track the distribution of gangliosides in mice brain tissue that were exposed to a very low level of explosive detonations (2.5-5.5 psi peak overpressure). The authors observed major increases of the ganglioside GM2 in the hippocampus, thalamus, and hypothalamus after a single blast exposure. Moreover, these changes were accompanied by depletion of ceramides. No neurological or brain structural signs of injury could be inferred using standard light microscopic techniques. The first source of variability is generated by the blast itself, whatever the distance or the time after the blast, while the second is the distance from the blast. These findings suggest that subtle molecular changes in intracellular membranes and plasmalemma compartments may be biomarkers for biological responses to mild bTBI. This is also the first report of a GM2 increase in the brains of mature mice from a non-genetic etiology. Woods AS, Colsch B, Jackson SN, Post J, Baldwin K, Roux A, Hoffer B, Cox BM, Hoffer ME, Rubovitch V, Pick CG, Schultz JA, Balaban C. Gangliosides and ceramides change in a mouse model of blast induced traumatic brain injury ACS Chem. Neurosci., e-pub 08 Jan 2013.

MALDI /Post Ionization-Ion Mobility Mass Spectrometry Of Noncovalent Complexes Of Dopamine Receptors' Epitopes Protein domains involved in receptor heteromer formation are disordered and rich in the amino acids necessary for the formation of noncovalent complexes (NCX). We present mass spectral NCX data from proteins and protein receptors' epitopes obtained by combining ion mobility (IM) and MALDI. Our main focus are NCX involved in heteromer formation occurring between epitopes of the Dopamine D_2 (D_2R) and Adenosine A_{2A} receptors ($A_{2A}R$) as well as D_2R and the a2 nicotinic (NR) receptor's subunit. The IM data yield information on the gas phase conformation of the singly charged NCX which are observed either directly from MALDI or as co-desorbed neutrals which are subsequently post-ionized by a time-delayed excimer laser pulse directed onto a portion of the neutral plume created by the MALDI desorption laser. Imaging mass spectrometry of the matrix/epitope dried droplet surface shows that the acidic and basic epitopes and their NCX are found to be spatially collocated within regions as small as 25x50 microns. Subtle differences in the relative abundance of protonated and cationized NCX and epitopes are measured in spatial regions near the sodium rich outer border of the droplet. Woods AS, Jackson SN, Egan T, Lewis EK, Tabet JC and Schultz JA. MALDI /post ionization-ion mobility mass spectrometry of noncovalent complexes of dopamine receptors' epitopes. Journal of Proteome Research, e-pub March 7, 2013.

Behavioral Neurophysiology Science Section, Cellular Neurobiology Research Branch

Risk-Responsive Orbitofrontal Neurons Track Acquired Salience Decision making is impacted by uncertainty and risk (i.e., variance). Activity in the orbitofrontal cortex, an area implicated in decision making, covaries with these quantities. However, this activity could reflect the heightened salience of situations in which multiple outcomes-reward and reward omission-are expected. To resolve these accounts, rats were trained to respond to cues predicting 100%, 67%, 33%, or 0% reward. Consistent with prior reports, some orbitofrontal neurons fired differently in anticipation of uncertain (33% and 67%) versus certain (100% and 0%) reward. However, over 90% of these neurons also fired differently prior to 100% versus 0% reward (or baseline) or prior to 33% versus 67% reward. These responses are inconsistent with risk but fit well with the representation of acquired salience linked to the sum of cue-outcome and cue-no-outcome associative strengths. These results expand our understanding of how the orbitofrontal cortex might regulate learning and behavior. Ogawa M, van der Meer MA, Esber GR, Cerri DH, Stalnaker TA, Schoenbaum G. Risk-responsive orbitofrontal neurons track acquired salience. Neuron. 2013 Jan 23; 77(2): 251-258.

Electrophysiology Research Section, Cellular Neurobiology Research Branch

Synaptic Targets Of Δ9-Tetrahydrocannabinol In The Central Nervous System The availability of potent synthetic agonists for cannabinoid receptors has facilitated our understanding of cannabinoid actions on synaptic transmission in the central nervous system. Moreover, the ability of these compounds to inhibit neurotransmitter release at many central synapses is thought to underlie most of the behavioral effects of cannabinoid agonists. However, despite the widespread use and misuse of marijuana, and recognition of its potential adverse psychological effects in humans, comparatively few studies have examined the actions of its primary psychoactive constituent, Δ(9)-tetrahydrocannabinol (THC), at well-defined synaptic pathways. Here IRP scientists examine the recent literature describing the effects of acute and repeated THC exposure on synaptic function in several brain regions and explore the importance of these neurobiological

actions of THC in drug addiction. Hoffman AF, Lupica CR. Synaptic targets of Δ9-tetrahydrocannabinol in the central nervous system. Cold Spring Harb Perspect Med. 2012 Dec 3. doi:pii: cshperspect.a012237v1. 10.1101/cshperspect.a012237. [Epub ahead of print].

Chemistry and Drug Metabolism Section, Clinical Pharmacology and Therapeutics Research Branch

Development and Validation Of The First Liquid Chromatography-Tandem Mass Spectrometry Assay For Simultaneous Quantification Of Multiple Antiretrovirals In Meconium A novel method for the simultaneous quantification of 16 antiretroviral (ARV) drugs and 4 metabolites in meconium was developed and validated. Quantification of 6 nucleoside/ nucleotide reverse transcriptase inhibitors, 2 non-nucleoside reverse transcriptase inhibitors, 7 protease inhibitors, and 1 integrase inhibitor was achieved in 0.25 g of meconium. Specimen preparation included methanol homogenization and solid-phase extraction. Separate positive and negative polarity multiple reaction monitoring mode injections were required to achieve sufficient sensitivity. Linearity ranged from 10 to 75 ng/g up to 2500 ng/g for most analytes and 100-500 ng/g up to 25,000 ng/g for some; all correlation coefficients were ≥0.99. Extraction efficiencies from meconium were 32.8-119.5% with analytical recovery of 80.3-108.3% and total imprecision of 2.2-11.0% for all quantitative analytes. Two analytes with analytical recovery (70.0-138.5%) falling outside the 80-120% criteria range were considered semiquantitative. Matrix effects were -98.3-47.0% and -98.0-67.2% for analytes and internal standards, respectively. Analytes were stable (>75%) at room temperature for 24 h, 4 °C for 3 days, -20 °C for 3 freeze-thaw cycles over 3 days, and on the autosampler. Method applicability was demonstrated by analyzing meconium from HIV-uninfected infants born to HIV-positive mothers on ARV therapy. This method can be used as a tool to investigate the potential effects of in utero ARV exposure on childhood health and neurodevelopmental outcomes. Himes SK, Scheidweiler KB, Tassiopoulos K, Kacanek D, Hazra R, Rich K, Huestis MA. Development and validation of the first liquid chromatography-tandem mass spectrometry assay for simultaneous quantification of multiple antiretrovirals in meconium. Analytical Chemistry, 2013, e-pub Dec. 21, 2012.

Intravenous and Sublingual Buprenorphine and Norbuprenorphine Pharmacokinetics In Humans Prescribed sublingual (SL) buprenorphine is sometimes diverted for intravenous (IV) abuse, but no human pharmacokinetic data are available following high-dose IV buprenorphine. Plasma was collected for 72h after administration of placebo or 2, 4, 8, 12, or 16mg IV buprenorphine in escalating order (single-blind, double-dummy) in 5 healthy male non-dependent opioid users. Buprenorphine and its primary active metabolite, norbuprenorphine, were quantified by liquid chromatography-tandem mass spectrometry with limits of quantitation of 0.1μg/L. Maximum buprenorphine concentrations (mean±SE) were detected 10min after 2, 4, 8, 12, 16mg IV: 19.3±1.0, 44.5±4.8, 85.2±7.7, 124.6±16.6, and 137.7±18.8μg/L, respectively. Maximum norbuprenorphine concentrations occurred 10-15min (3.7±0.7μg/L) after 16mg IV administration. Buprenorphine concentrations increased in a significantly linear dose-dependent manner up to 12mg IV buprenorphine. Thus, previously demonstrated pharmacodynamic ceiling effects (over 2-16mg) are not due to pharmacokinetic adaptations within this range, although they may play a role at doses higher than 12mg. Huestis MA**,** Cone EJ, Pirnay SO, Umbricht A and Preston KL. Intravenous and sublingual buprenorphine and norbuprenorphine pharmacokinetics in humans. Drug Alcohol Dependence 2012, e-pub Dec. 13. 2012.

Prenatal Tobacco Exposure, Tobacco Biomarkers In Meconium and Neonatal Growth Outcomes The objectives of this study were to assess relationships between marker concentrations of tobacco in meconium and weekly self-reported maternal cigarette consumption, and prediction of neonatal growth outcomes. Pregnant mothers (n = 119) from a longitudinal maternal smoking and infant neurobehavioral study (Behavior and Mood in Babies and Mothers [BAM BAM]) provided daily tobacco smoking histories. Nicotine, cotinine, and trans-3'-hydroxycotinine concentrations were quantified in 111 neonatal meconium specimens by liquid chromatography-tandem mass spectrometry. Median self-reported third trimester smoking was 5.9 cigarettes per day among smokers. Meconium samples from infants born to non-smokers (n = 42) were negative for tobacco markers, while specimens from self-reported smokers (n = 41) were positive for (median, range) nicotine (50.1 ng/g, 3.9-294), cotinine (73.9 ng/g, 6.4-329), and trans-3'-hydroxycotinine (124.5 ng/g, 10.2-478). Quitters (n = 28) self-reported stopping smoking at gestational weeks 2-39. Four meconium specimens from quitters were positive for tobacco biomarkers. Reduced birth weight, length, and head circumference significantly correlated with presence of meconium markers but not with individual or total marker concentrations. Among quitters and smokers, reduced infant birth weight, head circumference, and gestational age correlated with total and average daily cigarette consumption in the second and third trimesters. Smoking cessation or reduction during pregnancy improved neonatal outcomes. The window of detection for tobacco in meconium appears to be the third trimester; however, low exposure in this trimester failed to be detected. These results will aid physicians in educating women who are pregnant or thinking about becoming pregnant on the negative consequences of smoking during pregnancy. In addition, infants at risk can be identified at birth to assist early intervention efforts. Himes SK, Stroud L, Stroud LR, Scheidweiler KB, Niaura RS, Huestis MA. Prenatal tobacco exposure, tobacco biomarkers in meconium and neonatal growth outcomes. Journal of Pediatrics 2012, e-pub Dec. 1, 2012.

Can Oral Fluid Cannabinoid Testing Monitor Medication Compliance and/or Cannabis Smoking During Oral THC and Oromucosal Sativex® Administration IRP researchers characterize cannabinoid disposition in oral fluid (OF) after dronabinol, synthetic oral Δ(9)-tetrahydrocannabinol (THC), and Sativex, a cannabis-extract oromucosal spray, and evaluate whether smoked cannabis relapse or Sativex compliance can be identified with OF cannabinoid monitoring. Five and 15mg synthetic oral THC, low (5.4mg THC, 5.0mg cannabidiol (CBD)) and high (16.2mg THC, 15.0mg CBD) dose Sativex, and placebo were administered in random order (n=14). Oral fluid specimens were collected for 10.5h after dosing and analyzed for THC, CBD, cannabinol (CBN), and 11-nor-9-carboxy-THC (THCCOOH). After oral THC, OF THC concentrations decreased over time from baseline, reflecting residual THC excretion from previously self-administered smoked cannabis. CBD and CBN also were rarely detected. After Sativex, THC, CBD and CBN increased greatly, peaking at 0.25-1h. Median CBD/THC and CBN/THC ratios were 0.82-1.34 and 0.04-0.06, respectively, reflecting cannabinoids' composition in Sativex. THCCOOH/THC ratios within 4.5h post Sativex were ≤1.6pg/ng, always lower than after oral THC and placebo. THCCOOH/THC ratios increased throughout each dosing session. CONCLUSIONS: Lack of measurable THC, CBD and CBN in OF following oral THC, and high OF CBD/THC ratios after Sativex distinguish oral and sublingual drug delivery routes from cannabis smoking. Low THCCOOH/THC ratios suggest recent Sativex and smoked cannabis exposure. These data indicate that OF cannabinoid monitoring can document compliance with Sativex pharmacotherapy, and identify relapse to smoked cannabis during oral THC medication but not Sativex treatment, unless samples were collected shortly after smoking. Lee D, Karschner EL, Milman G, Barnes AJ, Goodwin RS, Huestis MA. Can oral fluid cannabinoid testing monitor

medication compliance and/or cannabis smoking during oral THC and oromucosal Sativex® administration? Drug Alcohol Dependence 2012, e-pub Nov. 9. 2012.

Tolerance To Subjective and Cardiovascular Effects Of Oral THC In Male Cannabis Smokers Oral cannabinoids are taken for medicinal or recreational purposes, yet little is known about tolerance to their effects after high-dose extended exposure. The development of tolerance to effects of around-the-clock oral synthetic Δ9-tetrahydrocannabinol (THC) (20 mg every 3.5-6 h) was evaluated in 13 healthy male daily cannabis smokers residing on a secure research unit: 40 mg on Day 1; 100 mg on Days 2-4; 120 mg on Days 5-6. Systolic and diastolic blood pressure (BP), heart rate, and symptoms of subjective intoxication (100 mm visual-analogue scales, VAS) were assessed the morning of Day 1 (before any oral THC), and on Days 2, 4 and 6, every 30 min for 3 h after the first morning THC dose. Morning subjective intoxication ratings increased from Days 1 to 2, and then declined on Days 4 and 6. The morning THC dose increased intoxication ratings on Day 2, but had less effect on Days 4 and 6, a pattern consistent with tolerance. THC lowered BP and increased heart rate over the six days. Plasma THC and 11-OH-THC concentrations increased significantly over the first five days of dosing. Six days of around-the-clock, oral THC produced tolerance to subjective intoxication, but not to cardiovascular effects. Gorelick DA, Goodwin RS, Schwilke GW, Schwope DM, Darwin WD, Kelly DL, McMahon RP, Liu F, Ortemann-Renon C, Bonnet D, Huestis MA. Tolerance to subjective and cardiovascular effects of oral THC in male cannabis smokers. Journal of Analytical Toxicology 2012, e-pub Oct. 16.

Examining the Relationships Between Prenatal Methamphetamine Exposure, Early Adversity, and Child Neurobehavioral Disinhibition Methamphetamine use is a growing problem among pregnant women in the United States. Many negative consequences of methamphetamine use have been documented for the users, but little research has examined the long-term association between prenatal methamphetamine exposure (PME) and childhood outcomes. The current study examined the extent to which PME was predictive of childhood neurobehavioral disinhibition (ND), as well as the extent to which early adversity mediated this relationship. A sample of 320 mother-infant dyads (162 PME) was followed from birth through 6.5 years of age. ND was conceptualized as a two factor model consisting of deficits in (a) behavioral and emotional control, and (b) executive function. PME was associated with behavioral and emotional control at 5 years, which was associated with executive function deficits at 6.5 years. Early adversity (birth through year 3) significantly mediated the relationship between PME and ND. Associations with previous research and implications for prevention are discussed. (PsycINFO Database Record (c) 2012 APA, all rights reserved). Abar B, LaGasse LL, DeRauf C, Newman E, Shah R, Smith LM, Arria A, Huestis MA, Dellagrotta S, Dansereau LM, Neal C, Lester BM. Examining the relationships between prenatal methamphetamine exposure, early adversity, and child neurobehavioral disinhibition. Psychology of Addictive Behaviors 2012, e-pub Oct. 15, 2012.

Predictors Of Inadequate Prenatal Care In Methamphetamine-Using Mothers In New Zealand and the United States This study compared patterns of prenatal care among mothers who used methamphetamine (MA) during pregnancy and non-using mothers in the US and New Zealand (NZ), and evaluated associations among maternal drug use, child protective services (CPS) referral, and inadequate prenatal care in both countries. The sample consisted of 182 mothers in the MA-Exposed and 196 in the Comparison groups in the US, and 107 mothers in the MA-Exposed and 112 in the Comparison groups in NZ. Positive toxicology results and/or maternal report of MA use during pregnancy were used to identify MA use. Information about sociodemographics, prenatal care and prenatal substance use was collected by maternal interview. MA-use during pregnancy is

associated with lower socioeconomic status, single marital status, and CPS referral in both NZ and the US. Compared to their non-using counterparts, MA-using mothers in the US had significantly higher rates of inadequate prenatal care. No association was found between inadequate care and MA-use in NZ. In the US, inadequate prenatal care was associated with CPS referral, but not in NZ. Referral to CPS for drug use only composed 40 % of all referrals in the US, but only 15 % of referrals in NZ. In the present study population, prenatal MA-use and CPS referral eclipse maternal sociodemographics in explanatory power for inadequate prenatal care. The predominant effect of CPS referral in the US is especially interesting, and should encourage further research on whether the US policy of mandatory reporting discourages drug-using mothers from seeking antenatal care. Wu M, LaGasse LL, Wouldes T, Arria AM, Wilcox T, Derauf C, Newman E, Shah R, Smith LM, Neal C, Huestis MA**,** Della Grotta, Lester BM. Predictors of inadequate prenatal care in methamphetamine-using mothers in New Zealand and the United States. Maternal and Child Health Journal 2013, Apr; 17(3): 566-575.

Impact Of Prolonged Cannabinoid Excretion In Chronic Daily Cannabis Smokers' Blood On "Per Se" Drugged Driving Law Cannabis is the illicit drug most frequently reported with impaired driving and motor vehicle accidents. Some "per se" laws make it illegal to drive with any amount of drug in the body, while others establish blood, saliva, or urine concentrations above which it is illegal to drive. The persistence of Δ-tetrahydrocannabinol (THC) in chronic daily cannabis smokers' blood is unknown. Thirty male chronic daily cannabis smokers resided on a secure research unit for up to 33 days, with daily blood collection. Samples were processed in an ice bath during sample preparation to minimize cannabinoid adsorption onto precipitant material. We quantified THC by 2-dimensional GC-MS. Of the 30 participants, 27 were THC-positive on admission, with a median (range) concentration of 1.4 μg/L (0.3-6.3). THC decreased gradually; only 1 of 11 participants was negative at 26 days, 2 of 5 remained THC-positive (0.3 μg/L) for 30 days, and 5.0% of participants had THC ≥1.0 μg/L for 12 days. Median 11-hydroxy-THC concentrations were 1.1 μg/L on admission, with no results ≥1.0 μg/L 24 h later. 11-Nor-9-carboxy-THC (THCCOOH) detection rates were 96.7% on admission, decreasing slowly to 95.7% and 85.7% on days 8 and 22, respectively; 4 of 5 participants remained THCCOOH positive (0.6-2.7 μg/L) after 30 days, and 1 remained positive on discharge at 33 days. Cannabinoids can be detected in blood of chronic daily cannabis smokers during a month of sustained abstinence. This is consistent with the time course of persisting neurocognitive impairment reported in recent studies. Bergamaschi MM, Karschner EL, Goodwin RS, Scheidweiler KB, Hirvonen J, Queiroz RHC. Impact of prolonged cannabinoid excretion in chronic daily cannabis smokers' blood on "per se" drugged driving laws. Huestis MA. Clinical Chemistry 2013, Mar; 59(3): 519-526.

Cannabis Effects On Driving Skills Cannabis is the most prevalent illicit drug identified in impaired drivers. The effects of cannabis on driving continue to be debated, making prosecution and legislation difficult. Historically, delays in sample collection, evaluating the inactive Δ-tetrahydrocannabinol (THC) metabolite 11-nor-9-carboxy-THC, and polydrug use have complicated epidemiologic evaluations of driver impairment after cannabis use. IRP scientists review and evaluate the current literature on cannabis' effects on driving, highlighting the epidemiologic and experimental data. Epidemiologic data show that the risk of involvement in a motor vehicle accident (MVA) increases approximately 2-fold after cannabis smoking. The adjusted risk of driver culpability also increases substantially, particularly with increased blood THC concentrations. Studies that have used urine as the biological matrix have not shown an association between cannabis and crash risk. Experimental data show that drivers attempt to compensate by driving more slowly after smoking cannabis, but control deteriorates with increasing task complexity. Cannabis

smoking increases lane weaving and impaired cognitive function. Critical-tracking tests, reaction times, divided-attention tasks, and lane-position variability all show cannabis-induced impairment. Despite purported tolerance in frequent smokers, complex tasks still show impairment. Combining cannabis with alcohol enhances impairment, especially lane weaving. Differences in study designs frequently account for inconsistencies in results between studies. Participant-selection bias and confounding factors attenuate ostensible cannabis effects, but the association with MVA often retains significance. Evidence suggests recent smoking and/or blood THC concentrations 2-5 ng/mL are associated with substantial driving impairment, particularly in occasional smokers. Future cannabis-and-driving research should emphasize challenging tasks, such as divided attention, and include occasional and chronic daily cannabis smokers. Hartman RL, Huestis MA. Cannabis effects on driving skills. Clinical Chemistry 2013, Mar; 59(3): 478-492.

Development Of the First Liquid Chromatography-Tandem Mass Spectrometry Assay For Antiretrovirals In Meconium A novel method for the simultaneous quantification of 16 antiretroviral (ARV) drugs and 4 metabolites in meconium was developed and validated. Quantification of 6 nucleoside/nucleotide reverse transcriptase inhibitors, 2 non-nucleoside reverse transcriptase inhibitors, 7 protease inhibitors, and 1 integrase inhibitor was achieved in 0.25 g of meconium. Specimen preparation included methanol homogenization and solid-phase extraction. Separate positive and negative polarity multiple reaction monitoring mode injections were required to achieve sufficient sensitivity. Linearity ranged from 10 to 75 ng/g up to 2500 ng/g for most analytes and 100-500 ng/g up to 25,000 ng/g for some; all correlation coefficients were ≥0.99. Extraction efficiencies from meconium were 32.8-119.5% with analytical recovery of 80.3-108.3% and total imprecision of 2.2-11.0% for all quantitative analytes. Two analytes with analytical recovery (70.0-138.5%) falling outside the 80-120% criteria range were considered semiquantitative. Matrix effects were -98.3-47.0% and -98.0-67.2% for analytes and internal standards, respectively. Analytes were stable (>75%) at room temperature for 24 h, 4 °C for 3 days, -20 °C for 3 freeze-thaw cycles over 3 days, and on the autosampler. Method applicability was demonstrated by analyzing meconium from HIV-uninfected infants born to HIV-positive mothers on ARV therapy. This method can be used as a tool to investigate the potential effects of in utero ARV exposure on childhood health and neurodevelopmental outcomes. Himes SK, Scheidweiler KB, Tassiopoulos K, Kacanek D, Hazra R, Borek N, Rich KC, and Huestis MA. Development of the first liquid chromatography-tandem mass spectrometry assay for antiretrovirals in meconium. Analytical Chemistry 2013 Feb 5; 85(3): 1896-1904.

Tolerance To Effects Of High-Dose Oral Δ9-Tetrahydrocannabinol and Plasma Cannabinoid Concentrations In Male Daily Cannabis Smokers Oral cannabinoids are taken for medicinal or recreational purposes, yet little is known about tolerance to their effects after high-dose extended exposure. The development of tolerance to effects of around-the-clock oral synthetic Δ9-tetrahydro-cannabinol (THC) (20 mg every 3.5-6 h) was evaluated in 13 healthy male daily cannabis smokers residing on a secure research unit: 40 mg on Day 1; 100 mg on Days 2-4; 120 mg on Days 5-6. Systolic and diastolic blood pressure (BP), heart rate, and symptoms of subjective intoxication (100 mm visual-analogue scales, VAS) were assessed the morning of Day 1 (before any oral THC), and on Days 2, 4 and 6, every 30 min for 3 h after the first morning THC dose. Morning subjective intoxication ratings increased from Days 1 to 2, and then declined on Days 4 and 6. The morning THC dose increased intoxication ratings on Day 2, but had less effect on Days 4 and 6, a pattern consistent with tolerance. THC lowered BP and increased heart rate over the six days. Plasma THC and 11-OH-THC concentrations increased significantly over the first five days of dosing. Six days of around-the-clock, oral THC produced tolerance to subjective intoxication, but not to

cardiovascular effects. Gorelick DA, Goodwin RS, Schwilke E, Schwope DM, Darwin WD, Kelly DL, McMahon RP, Liu F, Ortemann-Renon C, Bonnet D, Huestis MA. Tolerance to effects of high-dose oral δ9-tetrahydrocannabinol and plasma cannabinoid concentrations in male daily cannabis smokers. J Anal Toxicol. 2013, Jan-Feb; 37(1): 11-16.

The Effect Of Prenatal Methamphetamine Exposure On Attention As Assessed By Continuous Performance Tests: Results From The Infant Development, Environment, And Lifestyle Study The objectiveof this study was to assess for the increased risk of attention-deficit hyperactivity disorder (ADHD) in young children with prenatal methamphetamine exposure from the multicenter, longitudinal Infant Development, Environment, and Lifestyle (IDEAL) study. The IDEAL study enrolled 412 mother-infant pairs at 4 sites (Tulsa, OK; Des Moines, IA; Los Angeles, CA; and Honolulu, HI). Methamphetamine-exposed subjects (n = 204) were identified by self-report and/or gas chromatography/mass spectrometry confirmation of amphetamine and metabolites in infant meconium. Matched subjects (n = 208) denied methamphetamine use and had a negative meconium screen. This analysis included a subsample of 301 subjects who were administered the Conners' Kiddie Continuous Performance Test (K-CPT) at 5.5 years of age (153 exposed and 148 comparison). Hierarchical linear models adjusted for covariates tested exposure effects on K-CPT measures. Using the same covariates, logistic regression was used to determine the effect of exposure on the incidence of a positive ADHD confidence index score, defined as greater than 50%. There were no differences between the groups in omission or commission errors or reaction time for correct trials. However, methamphetamine exposure was associated with subtle differences in other outcomes predictive of ADHD, including increased slope of reaction time across blocks ($p < .001$), increased variability in reaction time with longer interstimulus intervals ($p < .01$), and increased likelihood of greater than 50% on the ADHD confidence index (odds ratio, 3.1; 95% confidence interval, 1.2-7.8; $p = .02$). Prenatal methamphetamine exposure was associated with subtle differences in K-CPT scores at 5.5 years of age. Even at this relatively young age, these children exhibit indicators of risk for ADHD and warrant monitoring. Kiblawi ZN, Smith LM, Lagasse LL, Derauf C, Newman E, Shah R, Arria A, Huestis MA, Dellagrotta S, Dansereau LM, Neal C, Lester BM. The effect of prenatal methamphetamine exposure on attention as assessed by continuous performance tests: results from the infant development, environment, and lifestyle study. Journal of Developmental and Behavioral Pediatrics 2013, Jan; 34(1): 31-37.

Prenatal Methamphetamine Exposure, Home Environment and Primary Caregiver Risk Factors Predict Child Behavior Problems At Five Years This study investigated the prospective association between prenatal methamphetamine (MA) exposure and child behavioral problems at 5 years while also examining the home environment at 30 months and several primary caregiver (PC) risk factors. Participants were 97 MA-exposed and 117 comparison children and their PCs enrolled in the Infant Development, Environment and Lifestyle Study. Hypotheses were that child behaviors would be adversely impacted by (a) prenatal MA exposure, (b) home environments that provided less developmental stimulation and emotional responsiveness to the child, and (c) the presence of PC psychological symptoms and other risk factors. Prenatal MA exposure was associated with child externalizing behavioral problems at 5 years. Home environments that were more conducive to meeting children's developmental and emotional needs were associated with fewer internalizing and externalizing behavioral problems. Independent of prenatal MA exposure, PC parenting stress and psychological symptoms were associated with increased child behavioral problems. Findings suggest prenatal MA exposure may contribute to externalizing behavioral problems in early childhood and the importance of considering possible vulnerabilities related to prenatal MA exposure in the context of the child's caregiving environment. Twomey JE, Lagasse LL, Derauf C,

Newman E, Shah R, Smith LM, Arria A, Huestis MA, DellaGrotta S, Roberts M, Dansereau L, Neal C, Lester BM. Prenatal methamphetamine exposure, home environment and primary caregiver risk factors predict child behavior problems at five years. American Journal of Orthopsychiatry 2013, Jan; 83(1): 64-72.

Co-Morbidity Of Substance Use Disorder and Psychopathology In Women Who Use Methamphetamine During Pregnancy In The US and New Zealand Methamphetamine (MA) abuse is a worldwide problem. Little is known about the co-morbidity of substance use disorders (SUD) and other psychiatric disorders of mothers who use MA prenatally. The Infant Development, Environment and Lifestyle (IDEAL) Study is a prospective, investigation of prenatal MA use and child outcome in the United States (US) and New Zealand (NZ). This study examined prenatal MA use and the co-morbidity of SUD and psychiatric disorders at 1-month postpartum. Mothers who used MA (US=127, NZ=97) were compared to a matched comparison group (US=193, NZ=110). The Substance Abuse Subtle Screening Inventory-3 was used to measure the probability of a SUD. The Brief Symptom Inventory (BSI) was used to measure the likelihood of a positive diagnosis of a psychiatric disorder. In the US and NZ, MA groups had lower SES, increased single parenting, delayed prenatal care, and increased polydrug use. In the US only, MA mothers had lower income than the comparison group. MA users were 10 times more likely to have a SUD and twice as likely to meet BSI criteria for a diagnosable psychiatric disorder. In NZ, but not the US, MA users were five times more likely to have co-morbidity of both. This disparity may be due to higher quantities of prenatal alcohol use associated with increased psychiatric symptoms. These findings suggest that addressing both substance abuse and psychiatric disorders in mothers who use MA may be required to effectively treat maternal MA use. Wouldes T, LaGasse LL, Derauf C, Newman E, Shah RZ, Smith LM, Arria AM, Huestis MA, Della Grotta S, Wilcox T, Neal CR, Jr, Lester BM. Co-morbidity of substance use disorder and psychopathology in women who use methamphetamine during pregnancy in the US and New Zealand. Drug Alcohol Dependence 2013, Jan 1; 127(1-3): 101-107.

Psychomotor Function In Chronic Cannabis Smokers During Sustained Abstinence The present study assessed psychomotor function in chronic, daily cannabis smokers during 3 weeks continuously monitored abstinence on a secure research unit. The authors hypothesized that psychomotor performance would improve during abstinence of chronic, daily cannabis smokers. Performance on the critical tracking (CTT) and divided attention (DAT) tasks was assessed in 19 male chronic, daily cannabis smokers at baseline and after 8, 14-16 and 21-23 days of continuously monitored abstinence. Psychomotor performance was compared to a control group of non-intoxicated occasional drug users. Critical frequency ($\lambda(c)$) of the CTT and tracking error and control losses of the DAT were the primary outcome measures. Results showed that chronic cannabis smokers' performance on the CTT ($p<0.001$) and the DAT ($p<0.001$) was impaired during baseline relative to the comparison group. Psychomotor performance in the chronic cannabis smokers improved over 3 weeks of abstinence, but did not recover to equivalent control group performance. Sustained cannabis abstinence moderately improved critical tracking and divided attention performance in chronic, daily cannabis smokers, but impairment was still observable compared to controls after 3 weeks of abstinence. Between group differences, however, need to be interpreted with caution as chronic smokers and controls were not matched for education, social economic status, life style and race. Bosker WM, Karschner EL, Lee D, Goodwin RS, Hirvonen J, Innis RB, Theunissen EL, Kuypers KPC, Huestis MA, Ramaekers JG. Psychomotor function in chronic cannabis smokers during sustained abstinence. PLoS One 2013; 8(1).

Perceived Child Behavior Problems, Parenting Stress, and Maternal Depressive Symptoms Among Prenatal Methamphetamine Users The present study was designed to examine parenting stress, maternal depressive symptoms, and perceived child behavior problems among mothers who used methamphetamine (MA) during pregnancy. Participants were a subsample (n = 212; 75 exposed, 137 comparison) of biological mothers who had continuous custody of their child from birth to 36 months. The subsample was drawn from a larger, ongoing longitudinal study on the effects of prenatal methamphetamine exposure (n = 412; 204 exposed, 208 comparison) (Arria et al in Matern Child Health J 10:293-302 2006). Mothers who used MA during pregnancy reported more parenting stress and more depressive symptoms than a matched comparison group. There were no differences between groups on perceived child behavior problems. In a hierarchical linear model, depressive symptoms, and perceived child behavior problems, but not MA exposure, were statistically significant predictors of parenting stress. Screening for potential parenting problems among mothers with a history of substance abuse is warranted. Parenting interventions targeting depressive symptoms, parenting stress, and child behavior problems are needed for this population. Liles BD, Newman E, Lagasse LL, Derauf C, Shah R, Smith LM, Arria AM, Huestis MA, Haning W, Strauss A, Dellagrotta S, Dansereau LM, Neal C, Lester BM. Perceived child behavior problems, parenting stress, and maternal depressive symptoms among prenatal methamphetamine users. Child Psychiatry and Human Development 2012, Dec; 43(6): 943-957.

Drug Design and Synthesis Section, Chemical Biology Research Branch

Increased Agonist Affinity At The M-Opioid Receptor Induced By Prolonged Agonist Exposure Prolonged exposure to high-efficacy agonists results in desensitization of the μ-opioid receptor (MOR). Desensitized receptors are thought to be unable to couple to G-proteins, preventing downstream signaling; however, the changes to the receptor itself are not well characterized. In the current study, confocal imaging was used to determine whether desensitizing conditions cause a change in agonist-receptor interactions. Using rapid solution exchange, the binding kinetics of fluorescently labeled opioid agonist, dermorphin Alexa594 (derm A594), to MORs was measured in live cells. The affinity of derm A594 binding increased after prolonged treatment of cells with multiple agonists that are known to cause receptor desensitization. In contrast, binding of a fluorescent antagonist, naltrexamine Alexa594, was unaffected by similar agonist pretreatment. The increased affinity of derm A594 for the receptor was long-lived and partially reversed after a 45 min wash. Treatment of the cells with pertussis toxin did not alter the increase in affinity of the derm A594 for MOR. Likewise, the affinity of derm A594 for MORs expressed in mouse embryonic fibroblasts derived from arrestin 1 and 2 knock-out animals increased after treatment of the cells with the desensitization protocol. Thus, opioid receptors were "imprinted" with a memory of prior agonist exposure that was independent of G-protein activation or arrestin binding that altered subsequent agonist-receptor interactions. The increased affinity suggests that acute desensitization results in a long-lasting but reversible conformational change in the receptor. Birdsong WT, Arttamangkul S, Clark MJ, Cheng K, Rice KC, Traynor JR, Williams, JT. Increased agonist affinity at the μ-opioid receptor induced by prolonged agonist exposure. J Neurosci 2013; 33(9): 4118-4127.

TACR1 Gene Variation and Neurokinin 1 Receptor Expression Is Associated With Antagonist Efficacy In Genetically Selected Alcohol-Preferring Rats Genetic deletion or antagonism of the neurokinin 1 receptor (NK1R) decreases alcohol intake, alcohol reward, and stress-induced alcohol relapse in rodents, while TACR1 variation is associated with alcoholism in humans.

IRP scientists used L822429, a specific antagonist with high affinity for the rat NK1R, and examined whether sensitivity to NK1R blockade is altered in alcohol-preferring (P) rats. Operant alcohol self-administration and progressive ratio responding were analyzed in P-rats and their founder Wistar line. The authors also analyzed Tacr1 expression and binding and sequenced the Tacr1 promoter from both lines. Systemic L822429 decreased alcohol self-administration in P-rats but did not affect the lower rates of alcohol self-administration in Wistar rats. Tacr1 expression was elevated in the prefrontal cortex and the amygdala of P-rats. In central amygdala, elevated Tacr1 expression was accompanied by elevated NK1R binding. Central amygdala (but not prefrontal cortex) infusion of L822429 replicated the systemic antagonist effects on alcohol self-administration in P-rats. All P-rats, but only 18% of their founder Wistar population, were CC homozygous for a-1372G/C single nucleotide polymorphism. In silico analysis indicated that the Tacr1-1372 genotype could modulate binding of the transcription factors GATA-2 and E2F-1. Electromobility shift and luciferase reporter assays suggested that the-1372C allele confers increased transcription factor binding and transcription. Genetic variation at the Tacr1 locus may contribute to elevated rates of alcohol self-administration, while at the same time increasing sensitivity to NK1R antagonist treatment. Schank JR, Tapocik JD, Barbier E, Damadzic R, Eskay RL, Sun H, Rowe KE, King CE, Yao M, Flanigan ME, Solomon MG, Karlsson C, Cheng K, Rice KC, Heilig M. Tacr1 gene variation and neurokinin 1 receptor expression is associated with antagonist efficacy in genetically selected alcohol-preferring rats. Biol Psychiat 2013, e-pub Feb. 15, 2013.

The Effects Of the 5-HT3 Receptor Antagonist Tropisetron On Cocaine-Induced Conditioned Taste Aversions Although cocaine readily induces taste aversions, little is known about the mechanisms underlying this effect. Recent work has shown that cocaine's actions on serotonin (5-HT) may be involved. To address this possibility, the present experiments examined a role of the specific 5-HT receptor, 5-HT_3, in this effect given that it is implicated in a variety of behavioral effects of cocaine. This series of investigations first assessed the aversive effects of the 5-HT_3 receptor antagonist tropisetron alone (Experiment 1). Specifically, in Experiment 1 male Sprague-Dawley rats were given repeated pairings of a novel saccharin solution and tropisetron (0, 0.056, 0.18 and 0.56mg/kg). Following this, a non-aversion-inducing dose of tropisetron (0.18mg/kg) was assessed for its ability to block aversions induced by a range of doses of cocaine (Experiment 2). Specifically, in Experiment 2 animals were given access to a novel saccharin solution and then injected with tropisetron (0 or 0.18mg/kg) followed by an injection of various doses of cocaine (0, 10, 18 and 32mg/kg). Cocaine induced dose-dependent taste aversions that were not blocked by tropisetron, suggesting that cocaine's aversive effects are not mediated by 5-HT, at least at this specific receptor subtype. At the intermediate dose of cocaine, aversions appeared to be potentiated, suggesting 5-HT_3 may play a limiting role in cocaine's aversive effects. These data are discussed in the context of previous examinations of the roles of serotonin, dopamine, and norepinephrine in cocaine-induced aversions. Briscione MA, Serafine KM, Merluzzi AP, Rice KC, Riley AL. The effects of the 5-HT3 receptor antagonist tropisetron on cocaine-induced conditioned taste aversions. Pharmacol Biochem Behav 2013, e-pub Feb. 13, 2013.

Effect Of Chronic Delivery Of the Toll-Like Receptor 4 Antagonist (+)-Naltrexone On Incubation Of Heroin Craving Recent evidence implicates toll-like receptor 4 (TLR4) in opioid analgesia, tolerance, conditioned place preference, and self-administration. Here, the authors determined the effect of the TLR4 antagonist (+)-naltrexone (a μ-opioid receptor inactive isomer) on the time-dependent increases in cue-induced heroin seeking after withdrawal (incubation of heroin craving). In an initial experiment, they trained rats for 9 hours per day to self-administer

heroin (.1 mg/kg/infusion) for 9 days; lever presses were paired with a 5-second tone-light cue. They then assessed cue-induced heroin seeking in 30-minute extinction sessions on withdrawal day 1; immediately after testing, they surgically implanted rats with Alzet minipumps delivering (+)-naltrexone (0, 7.5, 15, 30 mg/kg/day, subcutaneous) for 14 days. They then tested the rats for incubated cue-induced heroin seeking in 3-hour extinction tests on withdrawal day 13.
The authors found that chronic delivery of (+)-naltrexone via minipumps during the withdrawal phase decreased incubated cue-induced heroin seeking. In follow-up experiments, they found that acute injections of (+)-naltrexone immediately before withdrawal day 13 extinction tests had no effect on incubated cue-induced heroin seeking. Furthermore, chronic delivery of (+)-naltrexone (15 or 30 mg/kg/day) or acute systemic injections (15 or 30 mg/kg) had no effect on ongoing extended access heroin self-administration. Finally, in rats trained to self-administer methamphetamine (.1 mg/kg/infusion, 9 hours/day, 9 days), chronic delivery of (+)-naltrexone (30 mg/kg/day) during the withdrawal phase had no effect on incubated cue-induced methamphetamine seeking. The present results suggest a critical role of TLR4 in the development of incubation of heroin, but not methamphetamine, craving. Theberge FR, Li X, Kambhampati S, Pickens CL, St Laurent R, Bossert JM, Baumann MH, Hutchinson MR, Rice KC, Watkins LR, Shaham Y. Effect of chronic delivery of the toll-like receptor 4 antagonist (+)-naltrexone on incubation of heroin craving**.** Biol Psychiat 2013, e-pub Feb. 2, 2013.

Glucuronic Acid and the Ethanol Metabolite Ethyl-Glucuronide Cause Toll-Like Receptor 4 Activation and Enhanced Pain IRP scientists have previously observed that the non-opioid morphine metabolite, morphine-3-glucuronide, enhances pain via a toll-like receptor 4 (TLR4) dependent mechanism. The present studies were undertaken to determine whether TLR4-dependent pain enhancement generalizes to other classes of glucuronide metabolites. In silico modeling predicted that glucuronic acid alone and ethyl glucuronide, a minor but long-lasting ethanol metabolite, would dock to the same MD-2 portion of the TLR4 receptor complex previously characterized as the docking site for morphine-3-glucuronide. Glucuronic acid, ethyl glucuronide and ethanol all caused an increase in TLR4-dependent reporter protein expression in a cell line transfected with TLR4 and associated co-signaling molecules. Glucuronic acid-, ethyl glucuronide-, and ethanol-induced increases in TLR4 signaling were blocked by the TLR4 antagonists LPS-RS and (+)-naloxone. Glucuronic acid and ethyl glucuronide both caused allodynia following intrathecal injection in rats, which was blocked by intrathecal co-administration of the TLR4 antagonist LPS-RS. The finding that ethyl glucuronide can cause TLR4-dependent pain could have implications for human conditions such as hangover headache and alcohol withdrawal hyperalgesia, as well as suggesting that other classes of glucuronide metabolites could have similar effects.
Lewis SS, Hutchinson MR, Zhang Y, Hund DK, Maier SF, Rice KC, Watkins LR. Glucuronic acid and the ethanol metabolite ethyl-glucuronide cause toll-like receptor 4 activation and enhanced pain. Brain Behav Immun 2013, e-pub Jan. 21, 2013.

Patterns Of Nicotinic Receptor Antagonism II: Cardiovascular Effects In Rats Tobacco cessation pharmacotherapies currently are limited to nicotine itself, the partial nicotine agonists varenicline and cytisine, and the antidepressant bupropion. Compared with agonists, nicotinic antagonists such as the noncompetitive, nonselective compound mecamylamine, and the competitive, α4β2-preferring antagonist dihydro-β-erythroidine (DHβE) may be a novel approach to the treatment of tobacco smoking as both are effective antagonists of nicotine's central effects. Considering nicotinic acetylcholine receptors mediate critical peripheral effects of acetylcholine, such as cardiovascular effects, it is important to study how nicotinic antagonists would alter the cardiovascular system and the cardiovascular changes induced by nicotine. The effects of several

nicotinic agonists and antagonists on blood pressure and heart rate were measured in conscious, unrestrained rats following parenteral administration using a telemetry system. Nicotine and other nicotinic receptor agonists (epibatidine, varenicline, and cytisine) produced similar increases in blood pressure, whereas their effects on heart rate were biphasic. The cardiovascular changes were attenuated by the nonselective nicotine antagonist, mecamylamine, but the peripherally restricted antagonist hexamethonium blocked only the agonist-induced changes in blood pressure. The α7-preferring antagonist, MLA, and the α4β2-preferring antagonist, DHβE, were much less effective in blocking the agonist-induced cardiovascular changes, indicating that nicotine's cardiovascular effects, are due to activation at autonomic ganglia involving nicotinic receptor subtypes other than α4, α7, or β2. The data indicate that the cardiovascular effects of nicotine and nicotine-like agents are mediated through receptor mechanisms that are distinct from those that mediate the central effects of nicotine. Jutkiewicz EM, Rice KC, Carroll FI, Woods JH. Patterns of nicotinic receptor antagonism II: Cardiovascular effects in rats. Drug Alcohol Depend 2013, e-pub Jan. 17, 2013.

The NK1 Receptor Antagonist L822429 Reduces Heroin Reinforcement Genetic deletion of the neurokinin 1 receptor (NK1R) has been shown to decrease the reinforcing properties of opioids, but it is unknown whether pharmacological NK1R blockade has the same effect. Here, the authors examined the effect of L822429, a rat-specific NK1R antagonist, on the reinforcing properties of heroin in rats on short (1 h: ShA) or long (12 h: LgA) access to intravenous heroin self-administration. ShA produces heroin self-administration rates that are stable over time, whereas LgA leads to an escalation of heroin intake thought to model important dependence-related aspects of addiction. L822429 reduced heroin self-administration and the motivation to consume heroin, measured using a progressive-ratio schedule, in both ShA and LgA rats. L822429 also decreased anxiety-like behavior in both groups, measured on the elevated plus maze, but did not affect mechanical hypersensitivity observed in LgA rats. Expression of TacR1 (the gene encoding NK1R) was decreased in reward- and stress-related brain areas both in ShA and LgA rats compared with heroin-naïve rats, but did not differ between the two heroin-experienced groups. In contrast, passive exposure to heroin produced increases in TacR1 expression in the prefrontal cortex and nucleus accumbens. Taken together, these results show that pharmacological NK1R blockade attenuates heroin reinforcement. The observation that animals with ShA and LgA to heroin were similarly affected by L822429 indicates that the SP/NK1R system is not specifically involved in neuroadaptations that underlie escalation resulting from LgA self-administration. Instead, the NK1R antagonist appears to attenuate acute, positively reinforcing properties of heroin and may be useful as an adjunct to relapse prevention in detoxified opioid-dependent subjects. *Barbier E, Vendruscolo* LF, Schlosburg JE, Edwards S, Juergens N, Park PE, Misra KK, Cheng K, Rice KC, Schank J, Schulteis G, Koob GF, Heilig M. The NK1 receptor antagonist L822429 reduces heroin reinforcement. Neuropsychopharmacol 2012, e-pub Dec. 18, 2012.

Discriminative Stimulus Effects Of the GABAB Receptor-Positive Modulator Rac-BHFF: Comparison With GABAB Receptor Agonists and Drugs Of Abuse GABA(B) receptor-positive modulators are thought to have advantages as potential medications for anxiety, depression, and drug addiction. They may have fewer side effects than GABA(B) receptor agonists, because selective enhancement of activated receptors could have effects different from nonselective activation of all receptors. To examine this, pigeons were trained to discriminate the GABA(B) receptor-positive modulator (R,S)-5,7-di-tert-butyl-3-hydroxy-3-trifluoromethyl-3H-benzofuran-2-one (rac-BHFF) from its vehicle. The discriminative stimulus effects of rac-BHFF were not mimicked by the GABA(B) receptor agonists baclofen and γ-hydroxybutyrate (GHB), not by diazepam, and not by alcohol, cocaine, and nicotine, whose self-administration has been reported to

be attenuated by GABA(B) receptor-positive modulators. The discriminative stimulus effects of rac-BHFF were not antagonized by the GABA(B) receptor antagonist 3-aminopropyl (diethoxymethyl)phosphinic acid (CGP35348) but were attenuated by the less efficacious GABA(B) receptor-positive modulator 2,6-di-tert-butyl-4-(3-hydroxy-2,2-dimethylpropyl)phenol (CGP7930), suggesting the possibility that rac-BHFF produces its discriminative stimulus effects by directly activating GABA(B2) subunits of GABA(B) receptors. At a dose 10-fold lower than the training dose, rac-BHFF enhanced the discriminative stimulus effects of baclofen, but not of GHB. This study provides evidence that the effects of GABA(B) receptor-positive modulators are not identical to those of GABA(B) receptor agonists. In addition, the results suggest that positive modulation of GABA(B) receptors does not produce discriminative stimulus effects similar to those of benzodiazepines, alcohol, cocaine, and nicotine. Finally, the finding that rac-BHFF enhanced effects of baclofen but not of GHB is consistent with converging evidence that the populations of GABA(B) receptors mediating the effects of baclofen and GHB are not identical. Koek W, Cheng K, Rice KC. Discriminative stimulus effects of the GABAB receptor-positive modulator rac-BHFF: Comparison with GABAB receptor agonists and drugs of abuse. J Pharmacol Exp Ther 2013; 344(3): 553-560.

Z And E Rotamers Of N-Formyl-1-Bromo-4-Hydroxy-3-Methoxymorphinan-6-One And Their Interconversion As Studied By 1H/13C NMR Spectroscopy And Quantum Chemical Calculations N-Formyl-1-bromo-4-hydroxy-3-methoxymorphinan-6-one (compound 2), an important intermediate in the NIH Opiate Total Synthesis, presumably exists as a mixture of two rotamers (Z and E) in both CHCl(3) and DMSO at room temperature due to the hindered rotation of its N-C18 bond in the amide moiety. By comparing the experimental (1)H and (13)C chemical shifts of a single rotamer and the mixture of compound 2 in CDCl(3) with the calculated chemical shifts of the geometry optimized Z and E rotamers utilizing density functional theory, the crystalline rotamer of compound 2 was characterized as having the E configuration. The energy barrier between the two rotamers was also determined with the temperature dependence of (1)H and (13)C NMR coalescence experiments, and then compared with that from the reaction path for the interconversion of the two rotamers calculated at the level of B3LYP/6-31G*. Detailed geometry of the ground state and the transition states of both rotamers are given and discussed. Sulima A, Cheng K, Jacobson AE, Rice KC, Gawrisch K, Lee YS. Z and E rotamers of N-formyl-1-bromo-4-hydroxy-3-methoxymorphinan-6-one and their interconversion as studied by 1H/13C NMR spectroscopy and quantum chemical calculations**.** Magn Reson Chem 2013; 51(2): 82-88.

Molecular Neuropsychiatry Section, Molecular Neuropsychiatry Research Branch

Dietary Energy Intake Modifies Brainstem Autonomic Dysfunction Caused By Mutant A-Synuclein Parkinson's disease (PD) patients often exhibit impaired regulation of heart rate by the autonomic nervous system (ANS) that may precede motor symptoms in many cases. Results of autopsy studies suggest that brainstem pathology, including the accumulation of α-synuclein, precedes damage to dopaminergic neurons in the substantia nigra in PD. However, the molecular and cellular mechanisms responsible for the early dysfunction of brainstem autonomic neurons are unknown. Here the authors report that mice expressing a mutant form of α-synuclein that causes familial PD exhibit aberrant autonomic control of the heart characterized by elevated resting heart rate and an impaired cardiovascular stress response, associated with reduced parasympathetic activity and accumulation of α-synuclein in the brainstem. These ANS abnormalities occur early in the disease process. Adverse effects of α-synuclein on the control of heart rate are exacerbated by a

high energy diet and ameliorated by intermittent energy restriction. These findings establish a mouse model of early dysregulation of brainstem control of the cardiovascular system in PD, and further suggest the potential for energy restriction to attenuate ANS dysfunction, particularly in overweight individuals. Griffioen KJ, Rothman SM, Ladenheim B, Wan R, Vranis N, Hutchison E, Okun E, Cadet JL, Mattson MP. Dietary energy intake modifies brainstem autonomic dysfunction caused by mutant α-synuclein. Neurobiol Aging. 34(3):928-35, 2013.

Nicotine Psychopharmacology Section/Clinical Pharmacology and Therapeutics Branch

Nicotine Enhances Alerting, But Not Executive, Attention In Smokers And Nonsmokers Difficulty concentrating is a symptom of nicotine withdrawal that can contribute to relapse in individuals trying to quit smoking. The purpose of this study was to determine the effects of nicotine on executive and alerting attention in smokers and nonsmokers. Thirty daily smokers who were not tobacco deprived and 30 nonsmokers participated in the study. Participants received a single dose of intranasal nicotine (0, 0.5, or 1.5 mg) at each of 3 experimental sessions on separate days. Participants completed subjective ratings and 3 attention tasks before and after nicotine administration. Nicotine had no effect on executive attention as assessed by a Rapid Serial Visual Presentation (RSVP) task or the Attention Network Test in smokers and nonsmokers. In contrast, nicotine enhanced alerting attention by decreasing errors on a Continuous Performance Test (CPT) in nonsmokers and improving the correct identification of target words on the RSVP task in smokers. Nonsmokers were more sensitive than smokers to the subjective, but not the cardiovascular, effects of nicotine. The acute administration of intranasal nicotine improved alerting attention in nonsmokers as measured by the CPT, and in smokers as measured by the RSVP. Understanding the elements of attention enhanced by nicotine might guide the development of novel medications for tobacco dependence. Myers CS, Taylor RC, Salmeron BJ, Waters AJ, Heishman SJ. Nicotine enhances alerting, but not executive, attention in smokers and nonsmokers. Nicotine Tob Res. 2013; 15(1): 277-281.

Neurophysiology of Reward Seeking Section, Behavioral Neuroscience Research Branch

Optogenetic Inhibition Of Dorsal Medial Prefrontal Cortex Attenuates Stress-Induced Reinstatement Of Palatable Food Seeking In Female Rats Relapse to maladaptive eating habits during dieting is often provoked by stress. Recently, IRP scientists identified a role of dorsal medial prefrontal cortex (mPFC) neurons in stress-induced reinstatement of palatable food seeking in male rats. It is unknown whether endogenous neural activity in dorsal mPFC drives stress-induced reinstatement in female rats. Here, the authors used an optogenetic approach, in which female rats received bilateral dorsal mPFC microinjections of viral constructs coding light-sensitive eNpHR3.0-eYFP or control eYFP protein and intracranial fiber optic implants. Rats were food restricted and trained to lever press for palatable food pellets. Subsequently, pellets were removed, and lever pressing was extinguished; then the effect of bilateral dorsal mPFC light delivery on reinstatement of food seeking was assessed after injections of the pharmacological stressor yohimbine (an α-2 andrenoceptor antagonist) or pellet priming, a manipulation known to provoke food seeking in hungry rats. Dorsal mPFC light delivery attenuated yohimbine-induced reinstatement of food seeking in eNpHR3.0-injected but not eYFP-injected rats. This optical manipulation had no effect on pellet-priming-induced reinstatement or ongoing food-reinforced responding. Dorsal mPFC light delivery attenuated yohimbine-induced Fos immunoreactivity and disrupted neural activity during

in vivo electrophysiological recording in awake rats. Optical stimulation caused significant outward currents and blocked electrically evoked action potentials in eNpHR3.0-injected but not eYFP-injected mPFC hemispheres. Light delivery alone caused no significant inflammatory response in mPFC. These findings indicate that intracranial light delivery in eNpHR3.0 rats disrupts endogenous dorsal mPFC neural activity that plays a role in stress-induced relapse to food seeking in female rats. Calu DJ, Kawa AB, Marchant NJ, Navarre BM, Henderson MJ, Chen B, Yau H-J, Bossert JM, Schoenbaum G, Deisseroth K, Harvey BK, Hope BT, Shaham Y. Optogenetic inhibition of dorsal medial prefrontal cortex attenuates stress-induced reinstatement of palatable food seeking in female rats. Journal of Neuroscience. 2013; 33(1): 214-226.

Behavioral Neuroscience Section, Behavioral Neuroscience Branch

Dual Roles Of Dopamine In Food And Drug Seeking: The Drive-Reward Paradox The question of whether (or to what degree) obesity reflects addiction to high-energy foods often narrows to the question of whether the overeating of these foods causes the same long-term neuroadaptations as are identified with the late stages of addiction. Of equal or perhaps greater interest is the question of whether common brain mechanisms mediate the acquisition and development of eating and drug-taking habits. The earliest evidence on this question is rooted in early studies of brain stimulation reward. Lateral hypothalamic electrical stimulation can be reinforcing in some conditions and can motivate feeding in others. That stimulation of the same brain region should be both reinforcing and drive inducing is paradoxical; why should an animal work to induce a drive-like state such as hunger? This is known as the drive-reward paradox. Insights into the substrates of the drive-reward paradox suggest an answer to the controversial question of whether the dopamine system—a system downstream from the stimulated fibers of the lateral hypothalamus—is more critically involved in wanting or in liking of various rewards including food and addictive drugs. That the same brain circuitry is implicated in the motivation for and the reinforcement by both food and addictive drugs extends the argument for a common mechanism underlying compulsive overeating and compulsive drug taking. Wise RA. Dual roles of dopamine in food and drug seeking: The drive-reward paradox. Biol Psychiatry, e-pub Oct 5, 2012.

Heroin Self-Administration Experience Establishes Control Of Ventral Tegmental Glutamate Release By Stress and Environmental Stimuli Heroin and cocaine have very different unconditioned receptor-mediated actions; however, in the brain circuitry of drug-reward and motivation, the two drugs establish common conditioned consequences. A single experience with either drug can change the sensitivity of ventral tegmental area (VTA) dopamine neurons to glutamatergic input. In the case of cocaine, repeated intravenous self-administration establishes de novo VTA glutamate release and dopaminergic activation in response to conditioned stimuli and mild footshock stress. Here the authors determined whether repeated self-administration of heroin would establish similar glutamate release and dopaminergic activation. Although self-administration of heroin itself did not cause VTA glutamate release, conditioned glutamate release was seen when rats expecting rewarding heroin were given nonrewarding saline in its place. Mild footshock stress also caused glutamate release in heroin-trained animals. In each case, the VTA glutamate release was accompanied by elevations in VTA dopamine levels, indicative of dopaminergic activation. In each case, infusion of the ionotropic glutamate antagonist kynurenic acid blocked the VTA dopamine release associated with VTA glutamate elevation. Although glutamate levels in the extinction and reinstatement tests were similar to those reported in cocaine studies, the effects of heroin self-administration itself were quite different from what has been seen

during cocaine self-administration. Wang B, You Z-B, Wise RA. Heroin self-administration experience establishes control of ventral tegmental glutamate release by stress and environmental stimuli. Neuropsychopharmacology 2012; 37(13): 2863-2869.

Neurobiology of Relapse Section, Behavioral Neuroscience Branch

Effect Of Chronic Delivery Of The Toll-Like Receptor 4 Antagonist (+)-Naltrexone On Incubation Of Heroin Craving Recent evidence implicates toll-like receptor 4 (TLR4) in opioid analgesia, tolerance, conditioned place preference, and self-administration. Here the authors determined the effect of the TLR4 antagonist (+)-naltrexone (a μ-opioid receptor inactive isomer) on the time-dependent increases in cue-induced heroin seeking after withdrawal (incubation of heroin craving). In an initial experiment, we trained rats for 9 h/day to self-administer heroin (0.1 mg/kg/infusion) for 9 days; lever presses were paired with a 5-sec tone-light cue. They then assessed cue-induced heroin seeking in 30-min extinction sessions on withdrawal day 1; immediately after testing, we surgically implanted rats with Alzet minipumps delivering (+)-naltrexone (0, 7.5, 15, 30 mg/kg/day, s.c.) for 14 days. They then tested the rats for incubated cue-induced heroin seeking in 3-h extinction tests on withdrawal day 13. They found that chronic delivery of (+)-naltrexone via minipumps during the withdrawal phase decreased incubated cue-induced heroin seeking. In follow-up experiments, we found that acute injections of (+)-naltrexone immediately before withdrawal day 13 extinction test had no effect on incubated cue-induced heroin seeking. Furthermore, chronic delivery of (+)-naltrexone (15 or 30 mg/kg/day) or acute systemic injections (15 or 30 mg/kg) had no effect on ongoing extended access heroin self-administration. Finally, in rats trained to self-administer methamphetamine (0.1 mg/kg/infusion, 9 h/d, 9 days), chronic delivery of (+)-naltrexone (30 mg/kg/day) during the withdrawal phase had no effect on incubated cue-induced methamphetamine seeking. The present results suggest a critical role of TLR4 in the *development* of incubation of heroin, but not methamphetamine, craving. Theberge FR, Li A, Kambhampati S, Pickens, CL, Bossert JM, Baumann MH, Hutchinson MR, Rice RC, Watkins LR, Shaham Y (2013) Effect of chronic delivery of the Toll-like receptor 4 antagonist (+)-Naltrexone on incubation of heroin craving. Biol Psychiatry 2013, e-pub Feb 2, 2013. doi:pii: S0006-3223(13)00003-6.

MR Imaging and Spectroscopy Section, Neuroimaging Research Branch

Coupling Of Functional Connectivity and Regional Cerebral Blood Flow Reveals A Physiological Basis For Network Hubs Of the Human Brain Human brain functional networks contain a few densely connected hubs that play a vital role in transferring information across regions during resting and task states. However, the relationship of these functional hubs to measures of brain physiology, such as regional cerebral blood flow (rCBF), remains incompletely understood. Here, IRP researchers used functional MRI data of blood-oxygenation-level-dependent and arterial-spin-labeling perfusion contrasts to investigate the relationship between functional connectivity strength (FCS) and rCBF during resting and an N-back working-memory task. During resting state, functional brain hubs with higher FCS were identified, primarily in the default-mode, insula, and visual regions. The FCS showed a striking spatial correlation with rCBF, and the correlation was stronger in the default-mode network (DMN; including medial frontal-parietal cortices) and executive control network (ECN; including lateral frontal-parietal cortices) compared with visual and sensorimotor networks. Moreover, the relationship was connection-distance

dependent; i.e., rCBF correlated stronger with long-range hubs than short-range ones. It is notable that several DMN and ECN regions exhibited higher rCBF per unit connectivity strength (rCBF/FCS ratio); whereas, this index was lower in posterior visual areas. During the working-memory experiment, both FCS-rCBF coupling and rCBF/FCS ratio were modulated by task load in the ECN and/or DMN regions. Finally, task-induced changes of FCS and rCBF in the lateral-parietal lobe positively correlated with behavioral performance. Together, these results indicate a tight coupling between blood supply and brain functional topology during rest and its modulation in response to task demands, which may shed light on the physiological basis of human brain functional connectome. Liang X, Zou Q, He Y, Yang Y. Coupling of functional connectivity and regional cerebral blood flow reveals a physiological basis for network hubs of the human brain. Proc Natl Acad Sci U S A. 2013 Jan 29; 110(5): 1929-1934.

CART Peptide Induces Neuroregeneration In Stroke Rats Utilizing a classic stroke model in rodents, middle cerebral artery occlusion (MCAo), the authors describe a novel neuroregenerative approach using the repeated intranasal administration of cocaine- and amphetamine-regulated transcript (CART) peptide starting from day 3 poststroke for enhancing the functional recovery of injured brain. Adult rats were separated into two groups with similar infarction sizes, measured by magnetic resonance imaging on day 2 after MCAo, and were treated with CART or vehicle. The CART treatment increased CART level in the brain, improved behavioral recovery, and reduced neurological scores. In the subventricular zone (SVZ), CART enhanced immunolabeling of bromodeoxyuridine, a neural progenitor cell marker Musashi-1, and the proliferating cell nuclear antigen, as well as upregulated brain-derived neurotrophic factor (BDNF) mRNA. AAV-GFP was locally applied to the SVZ to examine migration of SVZ cells. The CART enhanced migration of GFP(+) cells from SVZ toward the ischemic cortex. In SVZ culture, CART increased the size of neurospheres. The CART-mediated cell migration from SVZ explants was reduced by anti-BDNF blocking antibody. Using (1)H-MRS (proton magnetic resonance spectroscopy), increases in N-acetylaspartate levels were found in the lesioned cortex after CART treatment in stroke brain. Cocaine- and amphetamine-regulated transcript increased the expression of GAP43 and fluoro-ruby fluorescence in the lesioned cortex. In conclusion, our data suggest that intranasal CART treatment facilitates neuroregeneration in stroke brain. Luo Y, Shen H, Liu HS, Yu SJ, Reiner DJ, Harvey BK, Hoffer BJ, Yang Y, Wang Y. CART peptide induces neuroregeneration in stroke rats. J Cereb Blood Flow Metab. 2013 Feb; 33(2): 300-310.

FUNCTIONAL INTEGRATION

Functional Integration (FI): Although the planned structural reorganization of the NIH institutes supporting addiction-related research did not go forward, the call for a "functional integration" is being realized with the creation of a strong collaborative framework to enhance and expand activities related to substance use, abuse, and addiction research. Functional integration will enable ICs [especially NIDA, the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the National Cancer Institute (NCI)] to pool resources and expertise and better capitalize on synergies in addiction science, address research opportunities, and meet public health needs.

New FOAs Issued that Support the FI

On January 30, 2013, NIDA issued an RFA entitled **Prevention and Health Promotion Interventions to Prevent Alcohol and Other Drug Abuse and Associated Physical and Psychological Health Problems in U.S. Military Personnel, Veterans and their Families (R01)** **RFA-DA-13-012** **(R34)** **RFA-DA-13-013**. The purpose of this RFA is to accelerate research on health promotion and prevention interventions with foci on reducing the onset and progression of alcohol, tobacco, and other drug use and abuse (including illicit and prescription drugs) and associated mental and physical health problems and on the promotion of health-enhancing behaviors among active-duty or recently separated (e.g., Iraq and Afghanistan) military troops, Veterans, and their families. Open date: April 1, 2013. Application due date(s): May 1, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

On March 27, 2013, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Research on Comparative Effectiveness and Implementation of HIV/AIDS and Alcohol Interventions (R01)** **RFA-AA-13-003** **(R21)** **RFA-AA-13-004.** This new initiative seeks to advance knowledge of the effective implementation and comparative effectiveness of alcohol-focused interventions among HIV+ individuals. Multiple factors need to be investigated, including potentially important patient and provider characteristics, and the organizational, financial, and structural factors that facilitate or inhibit the delivery of evidence-based services for HIV+ individuals with a range of alcohol use disorders. Open date: April 29, 2013. Letter of Intent due date(s): April 29, 2013. Application due date(s): May 29, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): May 29, 2013, by 5:00 PM local time of applicant organization.

On April 12, 2013, NIAAA, with participation by NIDA, issued a PA entitled **Mechanisms of Alcohol and Nicotine Co-Addiction (R21)** **PA-13-193** **(R01)** **PA-13-194** which NIDA subsequently signed on to: **(NOT-DA-13-024); (NOT-DA-13-025).** This FOA encourages R21 or R01 applications from institutions/organizations that propose to study neurobiological and behavioral mechanisms contributing to concurrent alcohol and nicotine co-addiction. Open date: September 16, 2013. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply by 5:00 PM local time of applicant organization.

FI Highlight: Upcoming Meeting

NIDA (DCNBR) and NIAAA are co-sponsoring a workshop: **Building the Next Generation of Integrative Approaches for Understanding Comorbid Alcohol, Drug Abuse, and Attention Disorders** in Rockville, MD – May 13-14, 2013.

PROGRAM ACTIVITIES/FOAS

New NIDA RFAs

On March 1, 2013, NIDA issued an RFA entitled **Short-term Mentored Career Enhancement Awards in the Basic Behavioral and Social Sciences (b-BSSR): Cross-Training at the Intersection of Animal Models and Human Investigation (K18) RFA-DA-14-002**. This funding mechanism will support development of research capability in b-BSSR, with specific emphasis on cross-training and establishing collaborations between researchers with expertise in animal models of basic behavioral and social processes and those studying similar or related processes in human subjects. Open date: November 11, 2013. Application due date(s): December 11, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

On March 20, 2013, NIDA issued an RFA entitled **Advancing Exceptional Research on HIV/AIDS (R01) RFA-DA-14-003**. This RFA will support highly innovative R01 applications on HIV/AIDS and drug abuse and will complement the Avant-Garde Award Program for HIV/AIDS research. The RFA focuses on innovative research projects that have the potential to open new areas of HIV/AIDS research and/or lead to new avenues for prevention and treatment of HIV/AIDS among substance abusers. Open date: July 1, 2013. Application due date(s): August 1, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): August 1, 2013, by 5:00 PM local time of applicant organization

On April 26, 2013, NIDA issued an RFA entitled **Medications Development Centers of Excellence Cooperative Program (U54) RFA-DA-14-004**. This RFA solicits Specialized Center Cooperative Agreement (U54) applications to provide support for Medications Development Centers of Excellence (MDCE) with emphasis on clinical research directed towards the identification, evaluation, and development of safe and effective medications and biologics for treatment of substance use disorders (SUDs). Letter of Intent due date(s): July 15, 2013. Application due date(s): August 15, 2013. AIDS application due date(s): August 15, 2013.

New NIDA PAs

On March 28, 2013, NIDA issued a PAR entitled **NIDA Mentored Clinical Scientists Development Program Award in Drug Abuse and Addiction (K12) PAR-13-163.** This PAR encourages applications for institutional research career development (K12) programs that propose to support intensive supervised research training and career development experiences for clinician scientists (scholars) leading to research independence in the area of drug abuse and addiction. Open date: May 12, 2013. Application due date(s): June 12, 2013; June 12, 2014; June 12, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): September 7, 2013; September 7, 2014; September 7, 2015, by 5:00 PM local time of applicant organization.

On April 5, 2013, NIDA issued a PAR entitled **Drug Abuse Dissertation Research (R36) PAR-13-182.** The purpose of this PAR is to invite applications for support of drug abuse doctoral dissertation research. Open date: May 16, 2013. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

New FOAs Issued by the NIH Roadmap

On March 4, 2013, the NIH Common Fund issued a Roadmap RFA entitled **NIH Director's Biomedical Research Workforce Innovation Award: Broadening Experiences in Scientific Training (BEST) (DP7) RFA-RM-12-022**. The purpose of this is to seek, identify and support bold and innovative approaches to broaden graduate and postdoctoral training, such that training programs reflect the range of career options that trainees (regardless of funding source) ultimately may pursue and that are required for a robust biomedical, behavioral, social and clinical research enterprise. Open date: April 10, 2013. Letter of Intent due date(s): April 10, 2013. Application due date(s): May 10, 2013 by 5:00 PM local time of applicant organization.. AIDS application due date(s): Not applicable.

On March 7, 2013, the NIH Common Fund issued a Roadmap RFA entitled **Planning Grants for the NIH Building Infrastructure Leading to Diversity (BUILD) Initiative (P20) RFA-RM-13-001**. The purpose of this FOA is to encourage organizations with experience in the mentorship of individuals underrepresented in the biomedical research workforce to submit planning grant applications for the NIH National Research Mentoring Network (NRMN). The NRMN will establish a nationwide consortium to provide networking and mentorship experiences for individuals from backgrounds underrepresented in biomedical research from the undergraduate to junior faculty level. Letter of Intent due date(s): April 10, 2013. Application due date(s): May 10, 2013. AIDS application due date(s): Not applicable.

On March 7, 2013, the NIH Common Fund issued a Roadmap RFA entitled **Planning Grants for the NIH National Research Mentoring Network (NRMN) (P20) RFA-RM-13-002**. The purpose of this FOA is to encourage institutions with expertise and innovative strategies for developing research and mentoring opportunities for undergraduate students from backgrounds underrepresented in biomedical research to submit applications for 6 month planning grants for the NIH Building Infrastructure Leading to Diversity (BUILD) initiative. The BUILD initiative aims to increase the diversity of the NIH-funded workforce by supporting collaborative programs that include novel approaches for enhancing undergraduate education, training, and mentorship, as well as infrastructure support and faculty development to facilitate those approaches. Letter of Intent due date(s): April 10, 2013. Application due date(s): May 10, 2013. AIDS application due date(s): Not applicable.

On April 2, 2013, the NIH Common Fund issued a Roadmap RFA entitled **Undiagnosed Diseases Gene Function Research (R21) RFA-RM-13-003**. The purpose of this FOA is to support gene function studies in collaboration with the Undiagnosed Diseases Network (UDN) building upon the NIH Intramural Research Program's Undiagnosed Diseases Program (NIH-UDP). Open date: May 14, 2013. Application due date(s): June 14, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

New Administrative Supplement Program Announcements Issued by NIH

On June 13, 2012, NIDA issued an administrative supplement entitled **Research on Marijuana Legalization in the US (Admin Supp) PA-13-138**. The NIDA announces the availability of administrative supplements to inform social, behavioral, and public health impacts of recent US marijuana legalization laws/policies. Open date(s): April 30, 2013. Application due date(s): May

31, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

On April 15, 2012, NIDA, in collaboration with numerous other NIH components, issued an administrative supplement entitled **NIH Administrative Supplements to Recover Losses Due to Hurricane Sandy Under the Disaster Relief Appropriations Act Non-Construction (Admin Supp)** **RFA-OD-13-199**. The purpose of this funding opportunity is for investigators and institutions impacted by Hurricane Sandy and with active NIH grants to request: 1) a 24-month extension of the current budget period, with 12-months of funding at the same funding level as the current year of the grant; and/or, 2a) one-time administrative supplements of up to $50,000 in direct costs (excluding consortium F&A costs) to replace lost and/or damaged research resources; and/or 2b) up to $100,000 to replace a single item of equipment so long as that request is accompanied by well-documented support for the need to replace that item of equipment. Open date(s): May 12, 2013. Application due date(s): June 12, 2013; January 14, 2014. AIDS application due date(s): June 12, 2013; January 14, 2014.

New RFAs Issued by Other NIH/HHS Components in which NIDA is a participant

On March 8, 2013, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Lasker Clinical Research Scholars Program (Si2) RFA-OD-13-004.** This RFA solicits applications for the Lasker Clinical Research Scholars Program for the purpose of supporting the research activities during the early stage careers of independent clinical researchers. Letter of Intent due date(s): May 24, 2013. Application due date(s): June 24, 2013. AIDS application due date(s): Not applicable.

On March 8, 2013, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Limited Competition - Multicenter AIDS Cohort Study: Center for the Coordination, Analysis, and Management of the MACS (CAMACS) (UM1) RFA-AI-13-010.** The purpose of this RFA is to renew the Center for the Coordination, Analysis, and Management of the Multicenter AIDS Cohort Study (CAMACS), and continue support for clinical, epidemiologic and basic research on a cohort of men who report sex with men (MSM). The MACS will continue to characterize the long-term, natural and treated history of HIV infection in MSM, provide insight into the clinical epidemiology of HIV, and further our understanding of predictors of disease among HIV positive MSM. Letter of Intent due date(s): June 11, 2013. Application due date(s): July 11, 2013. AIDS application due date(s): July 11, 2013.

On March 8, 2013, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Limited Competition Multicenter AIDS Cohort Study (MACS) Clinical Research Sites (U01) RFA-AI-13-011.** The purpose of this RFA is to renew the clinical research sites (CRSs) of the Multicenter AIDS Cohort Study (MACS) and continue support for clinical, epidemiologic and basic research on a cohort of men who report sex with men (MSM). The MACS will continue to characterize the long-term, natural and treated history of HIV infection in MSM, provide insight into the clinical epidemiology of HIV, and further our understanding of predictors of disease among HIV positive MSM. Open date: June 11, 2013. Letter of Intent due date(s): June 11, 2013. Application due date(s): July 11, 2013. AIDS application due date(s): July 11, 2013, by 5:00 PM local time of applicant organization.

On March 12, 2013, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Pilot Projects on Sports-Related Brain and Spinal Cord Injury (R21) RFA-NS-13-014 (R03) RFA-NS-13-015.** This initiative will support pilot projects on sports-related traumatic brain injury and spinal cord injury. Open date: April 14, 2013. Letter of Intent due date(s): April 14, 2013. Application due date(s): May 14, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

On March 13, 2013, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Collaborative Research on Chronic Traumatic Encephalopathy and Delayed Effects of Traumatic Brain Injury: Neuropathology and Neuroimaging Correlation (U01) RFA-NS-13-013.** The initiative will support a multicenter, systematic and comprehensive investigation of the neuropathology of Chronic Traumatic Encephalopathy and the delayed effects of traumatic brain injury using postmortem biospecimens, and histological and neuroimaging tools as a foundation for future studies to develop in vivo diagnostics. Open date: April 14, 2013. Letter of Intent due date(s): April 14, 2013. Application due date(s): May 14, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

On March 20, 2013, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Limited Competition: Revision Applications for Basic Social and Behavioral Research on the Social, Cultural, Biological, and Psychological Mechanisms of Stigma (R01) RFA-MD-13-005.** This RFA encourages revision applications to incorporate basic research on behavioral and social mechanisms underlying stigma into active R01 research projects. Open date: July 2, 2013. Letter of Intent due date(s): July 2, 2013. Application due date(s): August 2, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): August 2, 2013.

On March 27, 2013, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Eradication of HIV-1 from CNS Reservoirs: Implications for Therapeutics (R01) RFA-MH-14-170 (R21) RFA-MH-14-171.** This RFA invites research grant applications to address the problem of HIV-1 persistence focused solely on the central nervous system (CNS) of HIV-infected persons treated with Highly Active Anti-Retroviral Therapy (HAART). Open date: August 17, 2013. Letter of Intent due date(s): August 17, 2013. Application due date(s): September 17, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): September 17, 2013, by 5:00 PM local time of applicant organization.

On April 15, 2013, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Limited Competition: Restoration of New Investigator Pilot Projects Adversely Affected by Hurricane Sandy (R21) RFA-OD-13-005.** This RFA solicits applications from research institutions damaged as a result of Hurricane Sandy for the purpose of supporting recovery and restoration of new and early stage investigator pilot research and data destroyed or damaged as a result of the hurricane. Open date: May 19, 2013. Letter of Intent due date(s): May 19, 2013. Application due date(s): June 19, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

New PAs Issued with Other NIH/HHS Components in which NIDA is a Participant

On February 1, 2013, NIDA, in collaboration with numerous other NIH components, issued a PAR entitled **NIH Summer Research Experience Programs (R25) PAR-13-104**. The purpose of the

NIH Summer Research Experience Program (referred to as the "Summer Research Program") is to provide a high quality research experience for high school and college students and for science teachers during the summer academic break. The NIH expects that such programs will: help attract young students to careers in science; provide opportunities for college students to gain valuable research experience to help prepare them for graduate school; and enhance the skills of science teachers and enable them to more effectively communicate the nature of the scientific process to their students. The programs would also contribute to enhancing overall science literacy. Open date(s): March 2, 2013. Application due date(s): April 2, 2013; April 2, 2014; April 2, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): May 21, 2013, May 21, 2014 and May 21, 2015 by 5:00 PM local time of applicant organization.

On February 15, 2013, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Mechanisms, Models, Measurement, & Management in Pain Research (R03) PA-13-117 (R01) PA-13-118 (R21) PA-13-119**. The purpose of this PA is to inform the scientific community of the pain research interests of the various Institutes and Centers (ICs) at the National Institutes of Health (NIH) and to stimulate and foster a wide range of basic, clinical, and translational studies on pain as they relate to the missions of these ICs. Open date(s): May 16, 2013. Application due date(s): Standard dates, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply, by 5:00 PM local time of applicant organization.

On March 6, 2013, NIDA, in collaboration with numerous other NIH components, issued a PAR entitled **High Throughput Screening (HTS) to Discover Chemical Probes (X01) PAR-13-134 (R03) PAR-13-135**. This Resource Access Opportunity is to promote and support discovery and development of new chemical probes as research tools for use by the research community to advance the understanding of biological functions and disease mechanisms. The announcement encourages partnership between assay submitters and a funded High Throughput Screening (HTS)/chemical probe discovery facility to conduct the joint research. Open date(s): March 4, 2013. Application due date(s): August 6, 2013; December 4, 2013; April 4, 2014; August 6, 2014; December 4, 2014; April 3, 2015; August 6, 2015; December 4, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

On March 8, 2013, NIDA, in collaboration with numerous other NIH components, issued a PAR entitled **Bioengineering Research Grants (BRG) (R01) PAR-13-137**. The purpose of this PAR is to encourage collaborations between the life and physical sciences that: 1) apply a multidisciplinary bioengineering approach to the solution of a biomedical problem; and 2) integrate, optimize, validate, translate or otherwise accelerate the adoption of promising tools, methods and techniques for a specific research or clinical problem in basic, translational, or clinical science and practice. Open date(s): May 5, 2013. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply.

On March 13, 2013, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Development of Highly Innovative Tools and Technology for Analysis of Single Cells (SBIR) (R43/R44) PA-13-140**. This PA encourages Small Business Innovation Research (SBIR) research grant applications to develop next-generation tools that distinguish heterogeneous states among cells and have commercial potential. Open date(s): July 5, 2013. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply.

On March 25, 2013, NIDA, in collaboration with numerous other NIH components, issued a PA/PAR entitled **Development and Application of PET and SPECT Imaging Ligands as Biomarkers for Drug Discovery and for Pathophysiological Studies of CNS Disorders (R21) PA-13-157 (R21/R33) PAR-13-158**. This PA/PAR invites research grant applications from organizations/institutions that propose the development of novel radioligands for positron emission tomography (PET) or single photon emission computed tomography (SPECT) imaging in human brain, and that incorporate pilot or clinical feasibility evaluation in pre-clinical studies, model development, or clinical studies. Open date(s): May 16, 2013. Application due date(s): Standard dates apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): Standard AIDS dates apply.

On April 25, 2013, NIDA, in collaboration with numerous other NIH components, issued a PAR entitled **Limited Competition: Fogarty HIV Research Training Program for Low-and Middle-Income Country Institutions (D43) PAR-13-126**. The purpose of this PAR is to encourage applications for research training programs to develop and strengthen the scientific leadership and expertise needed for HIV-related research at eligible Low-and Middle-Income Country (LMIC) institutions. Open date(s): June 24, 2013. Application due date(s): July 24, 2013, July 24, 2014, July 30, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): July 24, 2013, July 24, 2014, July 30, 2015 by 5:00 PM local time of applicant organization.

New NIH FOAs Issued in Collaboration with the FDA Center for Tobacco Products

No new FOAs issued in Collaboration with the FDA Center for Tobacco Products.

Other Program Activities

CTN Update

A total of 50 protocols have been initiated since 2001, including multi-site clinical trials (36), multi-site surveys (3), studies in special populations (5), and secondary analyses of data across various trials (6). In addition, 28 ancillary studies have been supported by CTN and non-CTN funds. Over 15,000 participants have been enrolled in CTN studies.
Information on protocols can be found at:
http://www.drugabuse.gov/about-nida/organization/cctn/ctn/research-studies

On March 13/14, 2013, DPMCDA held an Investigators Meeting to initiate a multi-site trial of nepicastat (a selective dopamine B-hydroxylase inhibitor) for the treatment of cocaine dependence. The trial is being supported through NIDA's Interagency Agreement with the VA Cooperative Studies Program. Details of the clinical trial design can be found at:
http://clinicaltrials.gov/ct2/show/NCT01704196?term=nepicastat+cocaine&rank=1

EXTRAMURAL POLICY AND REVIEW ACTIVITIES

Application Receipt, Referral, and Review

During the May 2013 Council Cycle, NIDA received 1366 applications (872 with NIDA as primary IC assignment). The Office of Extramural Affairs (OEA) managed the programmatic referral process for these applications.

OEA arranged and managed 18 Special Emphasis Panel (SEP) grant application review meetings in which 170 applications, (or 498 R01 equivalents[1]), were peer reviewed for scientific and technical merit.

In addition, OEA staff arranged and managed13 contract review meetings to evaluate 61 R&D contract proposals and one R&D contract concept[2]. Details are reported below in accordance with section 15.413-1 of the Federal Acquisition Regulation (FAR), which states: "none of the information contained in them or concerning the number or identity of offerors shall be made available to the public..." before the award. Thus, only if the contract has been awarded is the number of proposals received reported below.

Four hundred six (406) reviewers were recruited for these grant and contract reviews.

Special Emphasis Panel Reviews include

- Cognitive Remediation and Work Therapy (R01)
  - PA 10-012
  - n= 1
- Collaborative Clinical Trials (R01)
  - PAR 10-099
  - n= 2
- NIDA I/START Small Grant Review (R03)
  - PAR 12-066
  - n=10
- NIDA Research "Center of Excellence" Grant Program (P50)
  - PAR 10-189
  - n=10
- NIDA Core "Center of Excellence" Grant Program (P30)
  - PAR 10-220
  - n=7
- Multisite Trial of HCV Linkages for Methadone Patients (R01)
  - PAR12-066
  - n=2
- Cohort Studies of HIV/AIDS and Substance Abuse (U01)

[1] R01 equivalents are used by the NIH OER as a way to standardize understanding of review workload across sites of grant application review. Applications or meetings are weighted after applying factors of complexity, scope, urgency, etc. Only one 'weight' addition is applied to a given set of applications.

[2] There are no R01 equivalent weighting factors for R&D Contract reviews. However, they are also marked by factors which increase the workload of every R&D Contract review beyond that evident in a simple proposal count (e.g. time sensitive reviews, non-recurring review meetings, paper applications, and no page limits).

- RFA 12-222
- n=9

- AIDS Avant Garde (DP1 -Interview)
  - RFA DA 13-002
  - n = 6
- Advancing Exceptional Research on HIV/AIDS (R01)
  - RFA DA 13-008
  - n=13
- The Interplay of Substance Abuse and HIV-1 Infection on Glial Cell Function (R01 & R21)
  - RFA DA 13-010 and RFA DA 13-011
  - n=24 (17 +7)
- Conference Grant Review (R13)
  - PA 12-212 and PA 10-106
  - n=9
- Translational Research on Interventions for Adolescents in Juvenile Justice (U01)
  - RFA DA 13-009
  - n = 19
- Strategic Alliances for Medications Development to Treat Substance Use (U01)
  - PAS 12-122
  - n=5
- NIH Pathway to Independence (K99/R00)
  - PAR11-197
  - n= 8
- The Diversity-promoting Institutions Drug Abuse Research Program (DIDARP) (R24)
  - PAR 11-060
  - n=4
- Cutting Edge Basic Research Awards (CEBRA) (R21)
  - PAR12-086
  - n = 38
- Time Sensitive Drug Abuse Research (R01)
  - PAR12-297
  - n= 3
- NIDA I/START Small Grant Review (R03)
  - PAR12-066
  - n=10

<u>R&D Contract Reviews</u>

- Development of Predictive in vivo Screening Systems for Phenotypic Drug Discovery
  - N43DA-13-7786
  - Status: pre award
- Feasibility of Development of RNAi-based Therapeutics for Treatment of HIV
  - N44DA-13-8907
  - Status: pre award
- Video Gaming Targeting Relapse Prevention in Youth
  - N43DA-13-4417
  - Status: pre award
- At home destruction of prescription medication

- N43DA-13-4418
- Status: pre award

- Profile Screening and Predictive Toxicology
  - N01DA-13-8909
  - Status: pre award
- A Mobile Application to Help Patients Take Their Pill Medications as Prescribed
  - N43DA-13-2233
  - Status: pre award
- Smokescreen: Genetic Screening Tool for Tobacco Dependence
  - N44DA-13-7783
  - Status: pre award
- Synthetic Peptides: Purity Determination, Stability Testing & Quantitative
  - N01DA-13-7785
  - Status: pre award
- International Research and Training Support
  - N01DA-13-1151
  - Status: pre award
- Synthesis and Distribution of Drugs of Abuse and Related Compounds
  - N01DA-13-7784
  - Status: pre award
- Feedback-Regulated Naloxone Device to Prevent Opiate Overdose Deaths
  - N44DA-13-2228
  - Status: pre award
- Toxicological Evaluations of Potential Medications to Treat Drug Addiction
  - N01 DA-13-8911
  - Status: pre award

CTN-Related Review Activities

The Data and Safety Monitoring Board(s) met:

- January 7, 2013, to discuss progress of protocol CTN 0052, A Randomized Controlled Evaluation of Buspirone for Relapse-Prevention in Adults with Cocaine Dependence (BRAC)
- February 12, 2013, to review the final study report of protocol CTN-0044, Web-delivery of Evidence-Based, Psychosocial Treatment for Substance Use Disorders

Certificates of Confidentiality

NIH issues a Certificate of Confidentiality to protect identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. Certificates of Confidentiality may be granted for studies collecting information which, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research

objectives and promote participation in studies by assuring confidentiality and privacy to participants, and NIH encourages their appropriate use.

NIDA OEA issues Certificates of Confidentiality to NIH funded investigators and to non-federally funded investigators for drug abuse and other studies relevant to the NIDA mission. OEA processed 42 Certificate of Confidentiality applications in this Council period.

Privacy Officer Coordination Activities

The Privacy Act provides safeguards for information about individuals maintained in a system of records (i.e. retrievable by name or other identifying information). Records of grant applications, awards, and administration are subject to provisions of the Privacy Act.

NIDA OEA houses the Privacy Officer, who evaluated 1 incident that implicates the Privacy Act, HIPAA, or other Federal regulations which could adversely affect NIH staff or members of the public, expose them to harm, or undermine the public's trust in our ability to safeguard personal information.

OEA reviewed 4 SBIR or station support contracts to determine if human subjects were involved, and if so, if personally identifiable information was collected and maintained in a government system of records. In addition, OEA completed Privacy Impact Assessment for two new NIDA outward-facing websites.

The Privacy Act requires NIDA to publish, in the Federal Register, notice of NIDA systems of records, whereby we keep information about individuals which can be retrieved by name or other specific identifier. NIDA had six notices of systems of records which have been updated: two notices were no longer relevant and were archived, two were subsumed into the NIH umbrella system of records, and two were revised with current data (e.g. location of records, responsible program, etc).

OEA worked with the NIH OD and the NIDA ISSO team to pilot test a Data Loss Prevention product to assess risks to personally identifiable information (PII) in NIDA. Because this was a test, no incident reports were generated, but NIDA received valuable information about private data in personal computers, in databases, and in transit (i.e. email).

NIH Guide Publication System

OEA Serves as the NIDA coordinator and liaison for the NIH Guide Publication System, including the Early Notification System. We coordinated the development and publication of 12 NIDA FOAs, including two complex, multi-Institute RFAs:

- RFA- DA-13-012 (R01) and DA-13-013 (R34) - Prevention and Health Promotion Interventions to Prevent Alcohol and Other Drug Abuse and Associated Physical and Psychological Health Problems in U.S. Military Personnel, Veterans and their Families (NIDA, NIAAA and DoD).

- RFA-DA-14-002 - Short-term Mentored Career Enhancement Awards in the Basic Behavioral and Social Sciences: Cross-Training at the Intersection of Animal Models and Human Investigation (K18) (29 NIH ICs and Offices)

OEA Staff Training

Dr. Meena Hiremath completed the NIH Supervisory Essentials Training, March 2013

Dr. Jerry McLaughlin completed the NIH Supervisory Refresher Training, March 2013

Dr. Jose Ruiz achieved the Project Management Institute's Project Management Professional (PMP)® credential in March, 2013

Loretta Beuchert completed the NIH training: Writing Instructions for the eSubmission of Complex Applications, January 2013

Loretta Beuchert completed the NIH training: Understanding the Relationships Between the Funding Opportunity and the Application Forms in ASSIST, February 2013

CONGRESSIONAL AFFAIRS SECTION
(Prepared April 24, 2013)

APPROPRIATIONS

Last month, the President released the FY 2014 President's Budget. The sequester is not taken into account for purposes of this budget. For NIH, the FY 2014 request is $31.3 billion, an increase of $471 million, or 1.5 percent, over the enacted FY 2012 level. For NIDA, the FY 2014 request is $1.072 billion, an increase of $20.2 million, or approximately 2 percent over the enacted FY 2012 level.

113th CONGRESS

The most relevant committee-related information for NIDA is listed below.
Senate: In the Senate, primary focus is on the

- Committee on Appropriations (Subcommittee on Labor, Health and Human Services, and Education; Financial Services; and Commerce, Justice, Science;
- Committee on Health, Education, Labor, and Pensions (HELP);
- Committee on the Judiciary (Crime and Terrorism Subcommittee); and the
- Caucus on International Narcotics Control (this is an officially recognized Caucus, established by law in 1985).

House: In the House, primary focus is on the

- Committee on Appropriations (Subcommittee on Labor, Health and Human Services, Education, and Related Agencies);
- Committee on Energy and Commerce (Subcommittee on Health); and the
- Committee on Oversight and Government Reform.

Senate Committee on Appropriations -- Labor/HHS Subcommittee	
Democrats	**Republicans**
Tom Harkin, IA, Chair	Jerry Moran, KS (Ranking Member)
Patty Murray, WA	Thad Cochran, MS
Mary Landrieu, LA	Richard Shelby, AL
Dick Durbin, IL	Lamar Alexander, TN
Jack Reed, RI	Lindsey Graham, SC
Mark Pryor, AR	Mark Kirk, IL
Barbara Mikulski, MD	Mike Johanns, NE
Jon Tester, MT	John Boozman, AR
Jeanne Shaheen, NH	
Jeff Merkley, OR	

Senate Committee on Health, Education, Labor and Pensions	
Democrats	**Republicans**
Tom Harkin, IA, Chair	Lamar Alexander, TN
Barbara Mikulski, MD	Mike Enzi, WY
Patty Murray, WA	Richard Burr, NC
Bernie Sanders, VT	Johnny Isakson, GA
Robert Casey, PA	Rand Paul, KY

Kay Hagan, NC	Orrin Hatch, UT
Al Franken, MN	Pat Roberts, KS
Mike Bennet, CO	Lisa Murkowski, AK
Sheldon Whitehouse, RI	Mark Kirk, IL
Tammy Baldwin, WI	Tim Scott, SC
Chris Murphy, CT	
Elizabeth Warren, MA	

Senate Committee on the Judiciary – Crime and Terrorism Subcommittee	
Democrats	**Republicans**
Sheldon Whitehouse, RI, Chair	Lindsey Graham, SC, Ranking Member
Dianne Feinstein, CA	Ted Cruz, TX
Chuck Schumer, NY	Jeff Sessions, AL
Dick Durbin, IL	Mike Lee, UT
Amy Klobuchar, MN	

Senate Caucus on International Narcotics Control	
Democrats	**Republicans**
Dianne Feinstein, CA, Chair	Chuck Grassley, IA, Co-Chair
Chuck Schumer, NY	James Risch, ID
Tom Udall, NM	John Cornyn, TX
Sheldon Whitehouse, RI	

House Committee on Appropriations -- Labor/HHS Subcommittee	
Republicans	**Democrats**
Jack Kingston, GA, Chair	Rosa DeLauro, CT, Ranking Member
Rodney Alexander, LA	Lucille Roybal-Allard, CA
Mike Simpson, ID	Barbara Lee, CA
Steve Womack, AR	Mike Honda, CA
Chuck Fleischmann, TN	
David Joyce, OH	
Andy Harris, MD	

House Committee on Energy and Commerce – Health Subcommittee	
Republicans	**Democrats**
Joe Pitts, PA, Chair	Frank Pallone, NJ, Ranking Member
Michael Burgess, TX, Vice-Chair	John Dingell, MI
Ed Whitfield, KY	Eliot Engle, NY
John Shimkus, IL	Lois Capps, CA
Mike Rogers, MI	Jan Schakowsky, IL
Tim Murphy, PA	Jim Matheson, UT
Marsha Blackburn, TN	Gene Green, TX
Phil Gingrey, GA	G.K. Butterfield, NC
Cathy McMorris Rodgers, WA	John Barrow, GA
Leonard Lance, NJ	Donna Christensen, VI

Bill Cassidy, LA	Kathy Castor, FL
Brett Guthrie, KY	John Sarbanes, MD
Morgan Griffith, VA	Henry Waxman, CA
Bus Bilirakis, FL	
Renee Ellmers, NC	
Joe Barton, TX	
Fred Upton, MI	

House Committee on Oversight and Government Reform	
Republicans	**Democrats**
Darrell Issa, CA, Chair	Elijah Cummings, MD, Ranking Member
John Mica, FL	Eleanor Holmes Norton, DC
John Duncan, TN	John Tierney, MA
Patrick McHenry, NC	William Lacy Clay, MO
Jim Jordan, OH	Stephen Lynch, MA
Jason Chaffetz, UT	Jim Cooper, TN
Tim Walberg, MI	Gerald Connolly, MD
James Lankford, OK	Jackie Speier, CA
Justin Amash, MI	Matt Cartwright, PA
Paul Gosar, AZ	Mark Pocan, WI
Pat Meehan, PA	Tammy Duckworth, IL
Scott DesJarlais, TN	Danny Davis, IL
Trey Gowdy, SC	Peter Welch, VT
Blake Farenthold, TX	Tony Cardenas, CA
Doc Hastings, WA	Steve Horsford, NV
Cynthia Lummis, WY	Michelle Lujan Grisham, NM
Rob Woodall, GA	
Thomas Massie, KY	
Doug Collins, GA	
Mark Meadows, NC	
Kerry Bentivolio, MI	
Ron DeSantis, FL	

CONGRESSIONAL MEETINGS/BRIEFINGS

March 4, 2013, Congressman Joseph Kennedy – On March 4, Dr. Volkow met with newly-elected Representative Joseph Kennedy (D-MA). He invited her to his office to discuss drug abuse and addiction issues in general, with a particular focus on prescription drug abuse.

March 11, 2013, Capitol Hill Briefing – Military Personnel, Veterans, and Their Families: How Substance Abuse Research is Effecting Positive Change. This briefing was organized and sponsored by the Friends of NIDA and highlighted recent research relevant to military personnel, veterans and their families and efforts to address substance abuse issues in the military community. The briefing was the 18th in the coalition's Charles R. Schuster Educational Briefing Series on Capitol Hill, designed to educate policy makers about current initiatives and advancements in

science funded by NIDA. Cosponsored by the Congressional Addiction, Treatment and Recovery Caucus, the Congressional Caucus on Prescription Drug Abuse and 23 member organizations of the Friends of NIDA, the briefing was attended by over 100 congressional staff, federal agency staff and members of the science advocacy community.

Michael E. Kilpatrick, MD, deputy director for force health protection and readiness programs at the Department of Defense (DOD), opened the briefing with remarks about the invisible wounds of war. Having served as a physician for the U.S. Navy for 25 years, Kilpatrick spoke about the tremendous stressors of war. He then outlined research-based methods that are being developed at DOD to curb substance abuse among service members, veterans and their families, and current programs such as resilience training used by the Army and Marine Corps. Kilpatrick noted than an annual health assessment conducted by the Army revealed a high rate of self-reported problems with alcohol.

Wilson M. Compton, MD, MPE, director of NIDA's division of epidemiology, services and prevention research, delivered a presentation on the institute's current research portfolio on war stressors and substance use. Compton discussed stressors of the Iraq and Afghanistan wars and the disincentives to seek treatment for substance use disorders in the military, including possibility of discharge, reduced confidentiality of medical records, potential career consequences and stigma related to treatment. Data on the prevalence of substance abuse in the military populations show a higher rate of prescription drug abuse and alcohol use among service members than in the civilian population. Compton also presented on the relationship of alcohol misuse and PTSD, on research that suggests how traumatic brain injury may contribute to vulnerability for substance use disorders, and on the problem of opioid addiction after exposure to opiate medications for the treatment of chronic pain.

Following Compton's presentation were two research presentations by NIDA funded scientists, psychologists Abigail Gewirtz, PhD, associate professor at the University of Minnesota's Department of Family Social Science and Institute of Child Development and Kathleen M. Carroll, PhD, Albert E. Kent Professor of Psychiatry at the Yale University School of Medicine. Gewirtz presented an evaluation of After Deployment, Adaptive Parenting Tools (ADAPT), a web-enhanced parenting program for military families. ADAPT is designed to extend the reach of the Parent Management Training Oregon (PMTO) program, found to be effective in improving children's adjustment and reducing substance use in other populations. Data on the effectiveness of the 14-week long, web-enhanced, group-based program for troops returning from deployment, who have at least one child aged 5-12 years, showed that at eight-month follow-up, people who received the ADAPT intervention displayed lower levels of poor discipline, better couple adjustment, increased mindfulness and stronger parenting self-efficacy than those who did not receive the ADAPT intervention.

Carroll presented findings from substance abuse treatment studies showing that effective substance use intervention reduces co-occurring problems and their costs. Behavioral therapies, including motivational interviewing, contingency management, cognitive behavior and behavioral therapies for couples and families have been found effective across types of substance abuse, including smoking and abuse of alcohol, opioids, cocaine and marijuana. Carroll presented an integrative model of PTSD and substance use disorders treatment that addresses the issues simultaneously, focusing on connections between the two. Carroll emphasized the importance of bridging the gap between evidence-based therapies and VA practice, particularly the training of a large workforce,

barriers to adopting novel therapies in large systems and the use of technology to make science based therapies more available. Her presentation included preliminary data on the effectiveness of Computer Based Training for Cognitive Behavioral Therapy (CBT 4 CBT) with veterans.

Kilpatrick and Compton discussed a 2012 presidential executive order requiring DOD, VA and the Department of Health and Human Services to work together to expand suicide prevention strategies and take steps to meet the current and future demand for mental health and substance abuse treatment services for veterans, service members and their families. The executive order followed a 2012 Institute of Medicine (IOM) report, Substance Use Disorders in the U.S. Armed Forces, that recommended increased emphasis on efforts to prevent substance use disorders; development of strategies for identifying, adopting, implementing and disseminating evidence-based programs and best practices for substance abuse care; increasing access to care and strengthening the substance use disorders workforce.

In January of this year, NIDA announced a joint research initiative with DOD, the National Institute on Alcohol Abuse and Alcoholism and the National Center for Complementary and Alternative Medicine, titled "Prevention and Health Promotion Interventions to Prevent Alcohol and Other Drug Abuse and Associated Physical and Psychological Health Problems in U.S. Military Personnel, Veterans and their Families." The funding announcement includes two mechanisms of support, an R01 and an R34. Compton also noted standing funding opportunity announcements that NIDA has issued in conjunction with other NIH institutes, for research on children in military families and for research on prevention and health promotion interventions.

April 3, 2013, Congressman (and Appropriations Chairman) Hal Rogers (R-KY) – While at the second annual Rx Drug Summit, Dr. Volkow met with Representative Rogers to continue their regular discussion around prescription drug issues. They also met with several teens who had experienced a death in their family as the result of prescription drug addiction.

SOME BILLS OF INTEREST

HR 486 – On February 4, 2013, Representative William Keating (D-MA) introduced the Stop Tampering of Prescription Pills act of 2013, to amend the Food, Drug and Cosmetic Act to incentivize the development of abuse-deterrent drugs. The bill was referred to the Committee on Energy and Commerce.

HR 498 – On February 5, 2013, Representative Lucille Roybal-Allard (D-CA) introduced a bill to reauthorize the Sober Truth on Preventing Underage Drinking (STOP) Act. Representatives Rosa DeLauro (D-CT), and Frank Wolf (R-VA) were the only two original co-sponsors of the legislation. The bill was referred to the House Committee on Energy and Commerce.

HR 499 – On February 5, Representative Jared Polis (D-CO) introduced the Ending Federal Marijuana Prohibition Act of 2013, to generally decriminalize and change the way the Controlled Substances Act is applied to marijuana. The bill was referred to the Committee on the Judiciary, the Committee on Ways and Means, the Committee on Energy and Commerce, the Committee on Natural Resources, and the Committee on Agriculture.

HR 672 -- On February 13, 2013, Representative Nick Rahall (D-WV) introduced the Prescription Drug Abuse Prevention and Treatment Act of 2013, to provide for increased federal oversight of prescription opioid treatment and assistance to states in reducing opioid abuse, diversion, and deaths. The bill was referred to the Committee on Energy and Commerce and the Committee on the Judiciary. See also S 348.

HR 1263 – On March 19, 2013, Representative Doris Matsui (D-CA) introduced the Excellence in Mental Health Act, to increase access to community behavioral health services for all Americans and to improve Medicaid reimbursement for community behavioral health services. The bill was referred to the Committee on Energy and Commerce. See also S 264, S 265.

HR 1285 – On March 20, 2013, Representative Vern Buchanan (R-FL) introduced Safe Prescribing Act of 2013, to amend the Controlled Substances Act to make any substance containing hydrocodone a schedule II drug. The bill was referred to the Committee on the Judiciary. See also S 621.

HR 1523 – On April 12, 2013, Representative Dana Rohrbacher (R-CA) introduced the Respect State Marijuana Laws Act of 2013, to amend the Controlled Substances Act to provide for a new rule regarding the application of the Act to marijuana, and for other purposes. The bill was referred to the Committee on the Judiciary and the Committee on Energy and Commerce.

S 237 – On February 7, 2013, Senator Lisa Murkowski (R-AK) introduced the Advancing FASD Research, Prevention and Services Act, to amend the Public Health Service Act to reauthorize and extend the FAS prevention and services program, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions.

S 264 – On February 7, 2013, Senator Debbie Stabenow (D-MI) introduced the Excellence in Mental Health Act, to expand access to community mental health centers and improve the quality of mental health care for all Americans. The bill was referred to the Committee on Health, Education, Labor, and Pensions. See also S 265, HR 1263

S 265 – On February 7, 2013 Senator Jack Reed (D-RI) introduced Community-Based Mental Health Infrastructure Improvements Act, to amend the Public Health Service Act to provide grants for community-based mental health infrastructure improvement. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also S 264, HR 1263

S. 348 – On February 14, 2013, Senator John Rockefeller (D-WV) introduced the Prescription Drug Abuse Prevention and Treatment Act of 2013, to provide for increased federal oversight of prescription opioid treatment and assistance to states in reducing opioid abuse, diversion, and deaths. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also HR 672.

S. 621 – On March 20, 2013, Senator Joe Manchin (D-WV) introduced the Safe Prescribing Act of 2013, to amend the Controlled Substances Act to make any substance containing hydrocodone a schedule II drug. The bill was referred to the Committee on the Judiciary. See also HR 1285.

S. 644 – On March 21, 2013, Senator Robert Casey (D-PA) introduced the Preventing Abuse of Cough Treatments Act of 2013, to amend the Food, Drug, and Cosmetic Act to prevent the abuse of

dextromethorphan, and for other purposes. The bill was referred to the Committee on Health, Education, Labor, and Pensions.

INTERNATIONAL ACTIVITIES

Research Funding

RFA Issued for Innovative HIV/AIDS Research

NIDA has issued an RFA for innovative research projects on the prevention and treatment of HIV/AIDS among substance abusers. Designed to complement NIDA's existing Avant-Garde Award Program for HIV/AIDS Research, this RFA requires applicants to have a detailed research plan and preliminary data. NIH expects that $2 million will be available in fiscal year 2014 to fund two or three R01 grants. Applications are due August 1, 2013. For more information, see RFA-DA-14-003.

NIDA Seeks Applications to Develop Clinical Research Training Programs

NIDA is inviting U.S. and international institutions to design drug abuse research training programs for individuals training to become (1) a clinical researcher; (2) a clinician or service provider; or (3) both a researcher and a service provider. Applicants are encouraged to develop ways to recruit participants from low- and middle-income countries or areas experiencing drug use epidemics. NIDA expects that the R25 awards will not exceed $350,000 in total direct costs annually, for up to 5 years. The first application deadline is May 22, 2013; the funding opportunity announcement will be active until September 8, 2015. For more information, see PAR-13-084.

Research Results

Letter Calls for Increased Research on Inhalants

Members of the NIDA IP Inhalant Working Group have published a letter in the *Canadian Journal of Public Health* [103(6): 473] calling for increased qualitative and quantitative research on inhalant abuse. The letter cites recent findings that inhalants are often the first substance misused by young people, use among girls is increasing, and volatile substances are being marketed in parts of Mexico with the addition of appealing odorants, such as cinnamon or coconut. The journal's table of contents is available here.

Former DISCA Awardee and Colleagues Report Changes in Mexican Controls Reduced Methamphetamine Potency, Harm in United States

Former NIDA IP Distinguished International Scientist Octavio Campollo, M.D., M.Sci., Ph.D., Mexico, and colleagues report in *Drug and Alcohol Dependence* that Mexico's 2004 controls on ephedrine and pseudoephedrine changed the U.S. methamphetamine market. Restrictions on these precursor chemicals in Mexico resulted in widespread emergence of less potent methamphetamine and declines in prevalence and availability of the most potent type of the drug, which had dominated the U.S. market since the late 1980s. The authors found that U.S. methamphetamine treatment admissions declined between 2005 and 2010 and suggest that the emergence of less potent methamphetamine may have helped limit dependence. [Cunningham, J.K., et al. 2013. Mexico's precursor chemical controls: Emergence of less potent types of methamphetamine in the United States. *Drug Alcohol Depen*d. Apr 1;129(1-2):125-36. doi: 10.1016/j.drugalcdep.2012.10.001]

Meetings

NIDA Director Discusses Health Consequences of Drug Use at Consortium of Universities for Global Health Meeting

NIDA Director Nora Volkow, M.D., participated in a round table discussion by National Institutes of Health leaders during the Consortium of Universities for Global Health (CUGH) conference, held March 14–16, 2013 in Washington DC. Dr. Volkow discussed the prevalence of drug use, the societal and health consequences of substance use, and treatment medications. She addressed global challenges in treating drug abuse, including stigma, the gap between treatment demand and availability, and reluctance to provide pharmacotherapy in some criminal justice institutions and countries. Fogarty International Center Director Roger Glass, M.D., M.P.H., led the discussion about global health research and training initiatives among Dr. Volkow; National Institute of Allergy and Infectious Diseases Director Anthony Fauci, M.D., National Heart, Lung, and Blood Institute Deputy Director Susan Shurin, M.D.; and National Cancer Institute Director Douglas Lowy, M.D. CUGH includes universities in North America and their partner institutions in low- and middle-income countries. The members promote mutually beneficial, long-term partnerships to develop human capital, share knowledge, and strengthen institutional capabilities. They build interdisciplinary collaborations to address global health challenges through. For more information, visit http://www.cugh.org/.

CTN Workshops Feature Fellows' Research Reports and Grant Writing Tips

Two INVEST/CTN Drug Abuse Research Fellows presented their research during an international workshop at the CTN Steering Committee Meeting, March 14, 2013 in Bethesda, Maryland. Vivi Octavia Lubis, M.D., Indonesia, reported on drug use trends in Indonesia. With her mentor, George Woody, M.D., University of Pennsylvania, Dr. Lubis is testing the impact of Behavioral Drug and HIV Risk Reduction Counseling on use of amphetamine-type stimulants, risky behaviors, treatment retention, psychiatric symptoms, re-arrests, other drug use, employment, and quality of life. Jan Klimas, Ph.D., Ireland, reported on his fellowship with mentor Dennis McCarty, Ph.D., Oregon Health & Science University. Dr. Klimas is investigating screening and brief intervention for alcohol use disorders among methadone patients in primary care settings and comparing buprenorphine services in the United States with primary care methadone services in Ireland. Other speakers during the international research symposium included Mathew Young, Ph.D., Canada; Fabián Fiestas, M.D., Peru; Evan Wood, M.D., Ph.D., Canada; Roberto Mollica, M.D., Italy; and Rodrigo Marin, Ph.D., Mexico.

Fellowships

NIDA Welcomes Fellows at Orientation

NIDA IP fellows from around the world visited NIDA headquarters during an orientation January 31 and February 1, 2013. IP Director Steven W. Gust, Ph.D., and Associate Director Dale Weiss welcomed the 16 fellows. Participants included the Hubert H. Humphrey Drug Abuse Research Fellows from Virginia Commonwealth and Johns Hopkins universities. They were joined by scientists working with U.S. mentors through the INVEST Drug Abuse Research, INVEST/CTN Drug Abuse Research, and U.S.–Mexico Drug Abuse Prevention Research fellowship programs. NIDA officials who spoke with the fellows included: Geoffrey Laredo, M.P.A., OSPC; Peter Hartsock, Dr. Ph., Dionne Jones, Ph.D., Jacqueline Lloyd, Ph.D., M.S.W., and Richard Jenkins, Ph.D., DESPR; and Petra Jacobs, M.D., and Carmen Rosa, M.S., CTN. The fellows also toured the

National Library of Medicine and met with Myat Htoo Razak, M.B.B.S., M.P.H., Ph.D., of the Fogarty International Center.

Russian Researcher Named 2013 WHO/NIDA/CPDD International Traveling Fellow
Bulat Idrisov, M.D., Russia, has been selected as the 2013 WHO/NIDA/CPDD International Traveling Fellow. NIDA partners with the World Health Organization (WHO) and the College on Problems of Drug Dependence (CPDD) to provide support for a 1-week research visit with a NIDA grantee and participation in the NIDA International Forum and the CPDD Annual Scientific Meeting. Since 2009, Dr. Idrisov has been working with Steven Sussman, Ph.D., University of Southern California, to implement Project EX, an evidence-based youth smoking cessation program, in Russia. The fellowship will permit Drs. Idrisov and Sussman to complete manuscripts about Project EX and to continue their evolving research into social self-control, post-traumatic growth, and multiple addiction arenas. In addition to his work at the Bashkortostan State Medical University regional pediatrics hospital, Dr. Idrisov works with the university's Department of International Affairs, serving as a medical interpreter and cultural ambassador for visiting professors.

Prevention Program Run by Former NIDA Humphrey Fellow Honored
Uganda Youth Development Link (UYDEL) received the *Drug Control Addiction Award* from Edutainment Africa for its drug and substance abuse prevention programs. Former NIDA Hubert H. Humphrey Fellow Rogers Kasirye (2011-2012) is executive director of UYDEL. The nongovernmental organization conducts HIV and substance abuse prevention programs as well as rehabilitation and life skills training for children and young adults between the ages of 10 and 30. In late 2012, the group signed a memorandum of understanding with Mentor International and the Uganda Olympic Committee to develop and pilot a prevention program focused on sports activities. UYDEL also conducts programs on adolescent sexual and reproductive health and on child rights, which focus on sexual abuse, trafficking, commercial sexual exploitation, and labor issues for children. Mr. Kasirye and his staff also conduct social research, and he recently published *Children and Vulnerability in Uganda; Policy and Practice*. For more information about UYDEL, visit the website.

NIDA Fellow Named Senior Scientist at Indian Occupational Health Institute
Former INVEST/CTN and NIDA Hubert H. Humphrey Drug Abuse Research Fellow Amit Chakrabarti, M.D., has been named senior scientist and deputy director in the eastern division of the National Institute of Occupational Health at the Indian Council of Medical Research in Kolkata. He will be responsible for research on alcohol and other drug abuse and assist in occupational and environmental health prevention, treatment, and policy issues at the national and regional levels.

CTN INVEST Fellows

Since 2008, NIDA's International Program and the Clinical Trials Network (CTN) jointly offer fellowships to non-U.S. scientists. The international researcher works with a CTN mentor affiliated with one of the 13 CTN Nodes. Fellows may conduct their research in any aspect of the CTN research agenda on drug abuse and addiction, such as intervention research, clinical trials methodology, or drug abuse treatment, as well as HIV/AIDS prevention. To date, 14 scientists have completed their fellowships and have successfully continued their research in their countries and one is currently working on her project with her CTN mentor.

Farida Allaghi, Executive Director of the Mentor Arabia Foundation, visited with Ms. Dale Weiss, NIDA International Office, and Dr. Eve Reider, Prevention Research Branch, NIDA, on December 11, 2012. Mentor Arabia is a regional non-governmental Foundation which advocates for drug prevention among Arab children and youth.

Travel Support

NIDA Supports Researcher at WHO Meeting

The NIDA IP supported the participation of Elizabeth Byrnes, Ph.D., Tufts University, at the WHO Preclinical Prenatal Substance Use Review meeting held January 29 – February 1, 2013 in Washington, DC. The meeting was part of the WHO effort to develop guidelines for identifying and managing substance use by pregnant women.

International Visitors

Under the sponsorship of the U.S. Department of State International Visitors Leadership Program a group from Central and South American visited NIDA on March 1, 2013. The purpose of the visit to the U.S. was to examine the overall U.S. strategy to address the problem of illicit drug use in the U.S, with a primary focus on demand reduction efforts, to examine prevention efforts used to combat illegal drug use in schools, workplaces and communities and to provide an overview of the U.S. response, both public and private, to illicit drug use, including education strategies and treatment at the national, state and local levels. Dale Weiss, IP, Carmen Rosa, CCTN, Ruben Baler, OSPC, Rich Jenkins, DESPR, Dionne Jones, DESPR and Will Aklin, DCNBR were the NIDA staff that met with the visitors.

Other International Activities

In March 2013, Dr. Anto Bonci, IRP Director, was a speaker at a plenary session at the SIMPAR (Study in Multidisciplinary Pain Research) meeting in Pavia, Italy where he set up collaborations with a variety of scientists present at the meeting.

During the last four months, Dr. Yavin Shaham, IRP, gave invited lectures at the Israeli Society of Neuroscience meeting and also gave university seminars at Ben-Gurion, Haifa, and Bar-Ilan Universities (Israel).

Dr. Yavin Shaham was invited to serve as a committee member of a study section of the French National Funding Agency for Research (ANR) as a committee member (first meeting held in March 2013).

Dr. Elliott Stein, IRP, delivered a talk at the Center for Addiction and Mental Health, Toronto, Canada in February 2013 entitled 'Neuroimaging Genetic Biomarkers of Addiction'. The above Rose et al article was also the subject of a Commentary in Biological Psychiatry: Commentary: Addy, NA and Picciotto, MR: Nicotine, Striatum and Reward. Biological Psychiatry 73, 205-206, 2013.

The Philippines Department of Health and the Philippines Forensic Drug Testing Society invited Dr. Marilyn Huestis to the Philippines. She provided a full day workshop for more than 120 scientists in Manila.

Dr. Marilyn Huestis, IRP, was selected as a "Distinguished Visiting Scientist" at the University of Technology, Sydney, Australia. This prestigious award was given for her to travel to Australia and present public and University lectures.

An international grant-writing workshop at the CTN meeting featured presentations by several NIDA staff members and grantees. GRB Scientific Review Officer Nadine Rogers, Ph.D., discussed the NIH grant application and review process; IP Director Steven W. Gust, Ph.D., DPMCDA Deputy Director Ivan Montoya, M.P.H., M.D., and ARP Associate Director Lynda Erinoff, Ph.D., discussed funding opportunities within NIDA for international research; Marya Levintova, Ph.D., Fogarty International Center, discussed funding opportunities within NIH; and Walter Ling, M.D., UCLA, and Dr. Woody discussed their experiences with international projects.

Drs. Cheryl Anne Boyce, DCNBR, Samia Noursi, DCNBR, and Steve Gust, OD, provided expertise and facilitated a review of preclinical data of the effects of substance use in pregnancy by Dr. Elizabeth Byrnes (Tufts University) and Dr. Josephine Johns (UNC-Chapel Hill) for **Meeting of the Guidelines Development Group on the WHO Guidelines on the Identification and Management of Psychoactive Substance Use and Substance Use Disorders in Pregnancy** held at the WHO Regional Office for the Americas in Washington, DC on January 29 through February 2, 2013. Drs. Noursi and Gust represented NIDA at the meeting and NIDA's International program supported Dr Byrnes travel to attend and present at the meeting.

COMMUNICATIONS

PUBLICATIONS

NIDA Publications and Online Resources

Substance Abuse in the Military (DrugFacts)
Published March 2013.
Offers an overview of trends of drug use in the military and the special risks faced by this population. En Español

NIDA's Teen website (www.teens.drugabuse.gov) launched a new design.

CTN-Related Publications

Five editions of the CTN Bulletin Board were distributed. The Bulletin Board is an electronic report on the progress of the protocols, committees, and node activity in the CTN. The Bulletin has wide readership within and outside the CTN and NIDA.

Data from 27 CTN studies are now available on the NIDA Data Sharing Web Site http://www.nida.nih.gov/CTN/Data.html. Nearly, 2,000 data sets have been downloaded by researchers from 42 countries. These data sets are in compliance with HIPAA and CDISC (Clinical Data Interchange Standards Consortium) standards in support of the interoperability required by the NIH Roadmap. The CTN Data Share is also part of the Neuroscience Information Framework (NIF), which is a dynamic inventory of Web-based neuroscience resources: data, materials, and tools accessible via any computer connected to the Internet.

International Program-Related Publications

NIDA International Program E-News
February 2013 – This issue highlighted the visit to NIDA by the Director of the Federal Drug Control Service of Russia, the summary report on the European Union research project on Driving Under the Influence of Drugs, Alcohol and Medicines (DRUID), and a letter published in the *Canadian Journal of Public Health* by members of the IP Inhalant Working Group that called for increased qualitative and quantitative research on inhalant abuse. Other stories reported on the orientation for NIDA IP drug abuse research fellows and an award to the drug abuse prevention program run by former NIDA Hubert H. Humphrey Fellow Rogers Kasiyre, Uganda.

Other Publications By NIDA Staff

Boyce CA, Maholmes V. Attention to the neglected: Prospects for research on child neglect for the next decade. Child Maltreat 2013; 18(1): 65-68.

Bruehl S, Apkarian AV, Ballantyne JC, Berger A, Borsook D, Chen WG, Farrar JT, Haythornthwaite JA, Horn SD, Iadarola MJ, Inturrisi CE, Lao L, Mackey S, Mao J, Sawczuk A, Uhl GR, Witter J, Woolf CJ, Zubieta JK, Lin Y. Personalized medicine and opioid analgesic prescribing for chronic pain: Opportunities and challenges. J Pain. 2013 Feb; 14(2): 103-113.

Compton WM, Dawson DA, Conway KP, Brodsky M, Grant BF. Transitions in illicit drug use status over 3 years: a prospective analysis of a general population sample. American Journal of Psychiatry March 2013 [Epub ahead of print].

Compton WM, Throckmorton DC, Lurie P, Volkow ND. Expanded access to opioid overdose intervention: Research, practice and policy needs. Annals of Internal Medicine 2013; 168: 65-66.

Conway KP, Vullo GC, Nichter B, Wang J, Compton WM, Iannotti RJ, Simons-Morton B. Prevalence and patterns of polysubstance use in a nationally representative sample of 10th graders in the United States. Journal of Adolescent Health 2013 Feb 26 [Epub ahead of print].
Ghitza UE, Wu LT, Tai B. Integrating substance abuse care with community diabetes care: implications for research and clinical practice. Subst Abuse Rehabil. 2013 Jan 1; 4 :3-10. Epub 2013 Jan 11.

Purohit V, Rapaka R, Frankenheim J, Avila A, Sorensen R, Rutter J. National Institute on Drug Abuse symposium report: drugs of abuse, dopamine, and HIV-associated neurocognitive disorders/HIV-associated dementia. J Neurovirol. 2013 Mar 1. [Epub ahead of print] PMID: 23456951 [PubMed - as supplied by publisher].

Schulden JD, Compton WM. Epidemiologic highlights from the World Drug Report 2012. Bulletin of the International Federation of Psychiatric Epidemiology 2013; 11(1): 5-9.

Wiley TR, Maholmes V, Lynne-Landsman S. [Eds]; February, 2013. Special Issue: Advancing the next generation of applied developmental science. Applied Developmental Science. [Special Issue].

A LIFE Sciences Special Proceedings volume entitled “TRP channels, GPCRs, endolipids and natural products: A tetrad that makes sense”, by Rapaka RS, Purohit V, Schnur P, Rutter J. In the April, 2013 issue.

Foreword entitled “TRP channels, GPCRs, endolipids and natural products: A tetrad that makes sense,by Rapaka RS, Purohit V, Schnur P, Rutter J.; appeared in Life Sci. 2013 Mar 19; 92(8-9): 393.

MEETINGS AND CONFERENCES

Select Meetings and Conferences in Which NIDA Played A Significant Role

On February 4-7, 2013, NIDA participated in a number of sessions at the **Community Anti-Drug Coalitions of America (CADCA) National Leadership Forum**. Dr. Ruben Baler presented two workshops; one to CADCA’s youth leadership group titled, ***Giving Youth a Scientific Voice*** designed to empower young leaders with essential information about the connections between our brains and our behaviors, and the second to the general audience titled, ***Where Do Addictions Come From?*** Dr. Jack Stein, Dr. Gaya Dowling and Carol Krause participated in a “Power Session” on ***Using Science to Prevent Drug Abuse: What’s New From NIDA?*** This session highlighted some of the latest findings from NIDA-supported research of relevance to community coalitions. New educational resources developed by NIDA, such as the "Family Check-Up" and outcomes of the most recent National Drug Facts Week were presented. Lastly, Dr. Harold Perl and NIDA

researcher Dr. Richard Spoth presented, ***The PROSPER Model: Implementing Effective Prevention Interventions in Local Communities -- A National Institute on Drug Abuse (NIDA) Research-to-Practice Workshop***. NIDA also held an Invitational Forum to discuss and receive feedback on a draft of the proposed publication titled ***Early Childhood Interventions for the Prevention of Drug Abuse: A Research Guide.***

On February 26-27, 2013, Dr. Jag Khalsa, DPMCDA, and Dr. Wilson M. Compton, DESPR, participated in a **Technical Consultation on HCV Infection in Young IDUs** in Washington, DC. They worked with Dr. Ron Valdiserri, Deputy Asst. Sec Health, Ms. Corinna Dan and other members of OASH, non-federal academic researchers, federal scientists from NIAID, NIDDK, NIDA, CDC, and SAMHSA, and various public health officials form the Appalachian region states – an area hard hit by HCV infections in young IDUs. The meeting was co-funded by NIAID, NIDA, and SAMHSA, and discussions led to numerous recommendations for additional research. A manuscript co-authored by the participating federal staff is in preparation.

On March 9, 2013, Dr. Gayathri Dowling, Chief, Science Policy Branch, OSPC, participated on a panel "**Raising Meth Addiction Awareness through Film**" at the DC Independent Film Festival. The discussion followed the world premiere of METH HEAD, the first feature film to offer an honest and compelling portrayal of a methamphetamine addict. Other panelists included representatives from SAMHSA, Faces and Voices of Recovery, the Entertainment Industries Council, Jane Clark, the filmmaker, and John W. McLaughlin, one of the film's producers and the inspiration for the METH HEAD story.

On March 12, 2013, NIDA participated in the **14th annual Brain Awareness Week** activities at the National Museum of Health and Medicine. NIDA sponsored "**NIDA Brain Derby**," an interactive fast-moving game designed to teach children about drugs of abuse and neuroscience. Drs. Cathrine Sasek, Dave Thomas, Roger Sorensen, Mary Kautz, Rik Kline, and Dave White took part in the events.

On March 16, 2013, Dr. Joni Rutter, Acting Director, DBNBR, organized two symposia at the **Society for Research on Nicotine and Tobacco (SRNT)** to promote recent findings in basic science. **Symposium 1** – Bench to bedside: translation of basic, pre-clinical and -omics-based discovery to prevention and treatment of smoking and smoking related disease, with Drs.Thorgeir Thorgiersson, Laura Bierut, Chris Amos, and Andrew Bergen. **Symposium 2** – Mice to men: basic science and preclinical research informing drug discovery and development through novel molecular targets, with Drs. Marina Piccioto, Paul Kenny, Elliot Hong, and Ron Hart.

In April 2013, Operation Unite hosted the **Second Annual Prescription Drug Abuse Summit** to facilitate meaningful dialogue and cooperation in addressing the prescription drug abuse epidemic. Multiple stakeholders and representatives from Federal government, advocacy, and constituent organizations attended, drawing more than 800 participants. Sessions were organized into six educational tracks tailored to provide stakeholders timely and relevant information for their particular field. Keynote speakers included Congressmen Hal Rogers, Michael Grimm, Daniel Webster, Nick Rahall, and Bill Keating; ONDCP Director Gil Kerlikowske; CDC Director Thomas Frieden; FDA Administrator Margaret Hamburg; Mayor Michael Bloomberg; CSAP Director Fran Harding, DEA Deputy Assistant Administrator Joe Rannazzisi, Florida Attorney General Pam Bondi; and NIDA Director Nora Volkow.

On April 3 & 4, 2013, Drs. Lisa Onken, DCNBR, Wilson Compton, DESPR, and Varda Shoham, NIMH, co-chaired a meeting, "**Improving Smoking Cessation Treatment for People with Schizophrenia**," in Bethesda, MD. The meeting was co-sponsored by NIMH and NCI, and the planning committee included Drs. Bill Riley and Yvonne Hunt (NCI); Debra Grossman, Petra Jacobs, Ivan Montoya, Jeff Schulden, and Kay Wanke (NIDA); Susan Azrin, Amy Goldstein, Denise Juliano-Bult, & Sarah Morris (NIMH). The state of the science of smoking cessation treatment for individuals with schizophrenia was discussed, as well as gaps and opportunities in the field.

On April 25, 2013, NIDA sponsored a series of activities at the NSC and on the NIH main campus in recognition of **Take Your Child to Work Day**. In addition, this year NIMH partnered with NIDA to include two activities, **The Brain Collector**, which featured Archie Fobbs from the National Museum of Health and Medicine and **See Your BRAIN in Action**. NIDA and NIMH staff who developed and led the activities included Drs. Cathrine Sasek, Mary Kautz, Sheri Grabus, and Dave Thomas, as well as Stephanie Older, Quandra Scudder, Hirsch Davis and Phyllis Quartey-Ampofo.

The **National CTN Steering Committee Meetings** were held March 12-15, 2013 in Bethesda, Maryland. The following meetings convened:
CTN Minority Interest Group Workshop
China HIV Study
Psychopharmacotherapy Special Interest Group
Gender Special Interest Group Workshop
Design &Analysis Workshop
International Grant Writing Workshop and Forum
NIDA SBIRT Study
CTN 0037, STRIDE
CTN 0047, SMART-ED
Executive Committee
Steering Committee

On April 25 – 26, 2013, Flair Lindsey from NIDA's Special Populations Office (SPO) coordinated the **Research Development Seminar Series Workshop "Mock Review"** for early career scholars to learn about the NIH grant review process.

On May 14, 2013, Dr. Cathrine Sasek, Science Policy Branch, OSPC, gave a presentation titled "Update: Science Education Drug Abuse Partnership Award (SEDAPA)" at the annual NIH science education conference, "**NIH SciEd 2013: Annual Conference for NIH Science Education Projects Implementing the Framework for K-12 Education and the Next Generation Science Standards**." In addition, she participated with the NIH Office of Science Education in a National Science Teachers Association webinar titled "**Hands-on Life Science for Your Next Generation Science Standards (NGSS) Classroom**" on May 7, 2013.

Select Meetings/Conferences for which NIDA Staff Organized Symposia/ Presented

Dr. Joni Rutter, Acting Director, DBNBR, organized two symposia at the Society for Research on Nicotine and Tobacco (SRNT) to promote recent findings in basic science. Symposium 1-Bench to

bedside: translation of basic, pre-clinical and -omics-based discovery to prevention and treatment of smoking and smoking related disease, with Thorgeir Thorgiersson, Laura Bierut, Chris Amos, and Andrew Bergen. Symposium 2-Mice to men: basic science and preclinical research informing drug discovery and development through novel moelcuar targets, with Marina Piccioto, Paul Kenny, Elliot Hong, and Ron Hart.

Dr. John Satterlee, DBNBR, gave a presentation entitled "Using Epigenomics Data to Interpret Genome-Wide Association Studies" at the NIDA Genetics Consortium meeting, held on Dec 5, 2012 in Rockville, MD.

Drs. Vishnu Purohit and Rao Rapaka, DBNBR, organized a symposium on Cannabinoids, HIV Pathogenicity, and other Infectious Disease Processes at the 19th Society on NeuroImmune Pharmacology (SNIP) Conference, San Juan, Puerto Rico, April 3-6, 2013.

Dr. Dave Thomas, DBNBR, made a presentation to The National Institute of Dental and Craniofacial Research's Council on January 29th, 2013 in Bethesda MD, titled "NIH Pain Consortium Centers of Excellence in Pain Education."

Dr. Dave Thomas made a keynote presentation titled: "The NIH Pain Consortium's Centers of Excellence in Pain Education: Enhancing Interprofessional Pain Education in Medical, Nursing, Dental and Pharmacy Schools" at The Science of Pain and the Art of Healing; Eleventh Annual Interprofessional Spring Symposium, April 4th, 2013 in Biddeford, Maine.

Dr. Dave Thomas moderated a session titled: "Improving Pain Education in Medical, Pharmacy, Nursing, and Dental Schools in the United States," at the 2013 American Pain Society Annual Scientific Meeting, May 9th, 2013 in New Orleans, Louisiana.

Dr. Dave Thomas was invited as a discussant at the Pain Education Special Interest Group session at the 2013 American Pain Society Annual Scientific Meeting, May 9th, 2013 in New Orleans, Louisiana.

Dr. Wilson M. Compton, Director, DESPR, presented to the Law and Neuroscience Colloquium for Federal Judges and participated in the two day discussion groups, March 14-15, 2013, Palo Alto, California,

Drs. Jacqueline Lloyd and Augusto Diana, DESPR, presented a paper at SAMHSA Prevention Day, part the CADCA National Leadership Forum, on February 4, 2012. The paper was entitled, "Opportunities for Secondary Analysis of Data Collected from SAMHSA/CSAP and NIDA Supported National Cross-Site Evaluation Study of the SPF-SIG," and the presentation also included SAMHSA staff.

Dr. Cora Lee Wetherington, DCNBR and Women and Sex/Gender Differences Research Program Coordinator, gave an invited address at the first annual Women's Health Research Day event at the Medical University of South Carolina, April 18, 2013.

Drs. Cheryl Anne Boyce and Karen Sirocco, DCNBR, and Dr. Mariela Shirley (NIAAA) presented by webinar for the NIH Funding Workshop for the National Leadership Consortium in Sensory

Disabilities (NLCSD) hosted by Salus University on January 16, 2013 at the invitation of the U.S. Department of Education, Office of Special Education Programs.

On February 25, 2013 in Washington, DC, Dr. Cheryl Anne Boyce (NIDA) and Dr. Paula Goodwin (SAMSHA) moderated a break-out session on "Mental Health: Depression and Alzheimer's Disease" at the White House African American Health Care Town Hall. Secretary Kathleen Sebelius, HHS, gave opening remarks at this town hall on the Affordable Care Act.

Dr. Yu (Woody) Lin, DCNBR, was invited by the American Academy of Pain Medicine to organize and moderate a workshop session entitled "NIH Pain Research: Optimizing Funding through Grant Writing". The conference was held at the Society's 29th annual conference on April 11--14, 2013 in Ft Lauderdale, Florida.

Dr. Steven Grant, DCNBR, conducted a Grant Writing Workshop at the annual meeting of the Cognitive Neuroscience Society held April 13-16, 2013 in San Francisco, California.

Dr. James Bjork, DCNBR, gave a talk entitled "Drugs, Alcohol, and Your Brain" to youth under juvenile justice supervision at the Thomas J.S. Waxter Children's Center in Laurel MD, on Monday March 18, 2013.

Carmen Rosa, CCTN, organized a symposium, entitled "CTN Race &Ethnic Minorities Research" on March 12-13, 2013 to present and discuss results from a variety of studies in the CTN addressing Racial/Ethnic minorities. The meeting was co-chaired with Dr. Kathleen Burlew, University of Cincinnati and included presentations from 15 researchers from the CTN. The meeting was also attended by members of the NIDA Researchers and Scholars representing all minority groups.

In January 2013, Dr. Anto Bonci, Director, IRP, gave a lecture at Columbia University in New York.

In February 2013, Dr. Bonci he gave a talk at UCSF at the Gallo Center in San Francisco.
Dr. Jonathan Katz, IRP, was invited to present a seminar at the Department of Pharmacology and Physiology, Program in Drug Discovery & Development, Drexel University College of Medicine. His talk was entitled "A Novel Reinforcing Action of Sigmentia Receptor Agonists: Implications for Stimulant Self Administration and Addiction." January 22, 2013.

Dr. Carl Lupica, IRP, served as a scientific advisor on the board of directors, and on the program committee for the Winter Conference on Brain Research in Breckendridge Colorado, January 2013. At this conference Dr. Lupica gave a lecture entitled "DA control of lateral habenula output to ventral midbrain and its role in shaping reward signaling" in a session entitled "Physiology of identified inputs to dopaminergic neurons".

On February 21, 2013 Dr. Lupica gave an invited lecture entitled "DA control of lateral habenula output to ventral midbrain and its role in shaping reward signaling" at the National Institute on Alcohol Abuse and Alcoholism Intramural Research Program seminar series.

In March 2013, Dr. Lupica served on the graduate board of oral exam committee for Rebecca Fallon, a graduate student in the Department of Biology at The Johns Hopkins University, and participant in the NIH-Johns Hopkins graduate training partnership.

Dr. Marilyn Huestis, IRP, presented at Grand Rounds at the University of Florida School of Medicine in Gainesville, FL. She presented her recent research on chronic frequent cannabis smoking, changes in the brain as a result of this constant stimulation and resultant residual psychomotor impairment that accompany low residual Δ9-tetrahydrocannabinol concentrations in the body during sustained cannabis abstinence.

Dr. Geoffrey Schoenbaum, IRP, gave the Abraham Ribicoff annual lecture at Yale University.

Upcoming Conferences/Exhibits

American Psychiatric Association Annual Meeting – San Francisco, CA – May 18-22, 2013.
College on Problems of Drug Dependence (CPDD) Annual Scientific Meeting – San Diego, California – June 15–20, 2013.

Community and Press Events

January 28, 2013 - National Drug Facts Week events now in all 50 states
February 14, 2013 - Prevention efforts focused on youth reduce prescription abuse into adulthood
February 28, 2013 - Dr. Nora Volkow appeared with Katie Couric on her show *Katie* to answer questions about teen drug abuse.
March 14, 2013 - Prior marijuana use could increase addictive power of nicotine
March 26, 2013 - NIDA research shines light on a potential target for cocaine addiction
March 27, 2013 - Genes linked to hepatitis C viral clearance could lead to personalized treatments
April 3, 2013 - NIH study sheds light on how to reset the addicted brain

STAFF HIGHLIGHTS

Staff Honors and Awards

Dr. Donna Calu, IRP, was selected by the NIDA and NIA Women Scientists Advisor Committee for the 2013 Excellence in Scientific Research, NIDA Fellow Award and will give a lecture at the award ceremony.

Dr. Eliot Gardner, IRP, was elected to membership in the American Academy of Addiction Psychiatry and the Canadian Society of Addiction Medicine.

Dr. Eliot Gardner was given an Honor Award by the Office of the Director, NIH, "for assuring a future national and international role of the NIH Animal Care and Use Program."

Dr. Jag Khalsa, DPMCDA, received a plaque "Certificate of Appreciation" from Dr. Howard Koh, the Assistant Secretary for Health, DHHS, for contributions towards the implementation of the Viral Hepatitis Action Plan, especially on the subject of an emerging epidemic of HCV infection in young IDUs.

Ms. Dayong Lee, MS, IRP received the June K. Jones Award from the American Academy of Forensic Sciences in February 2013 for her excellent research on oral fluid cannabinoids. Ms. Lee is defending her doctoral dissertation in June 2013 from the University of Maryland School of Medicine and Dr. Huestis is her primary mentor. All of her research was performed in the Chemistry and Drug Metabolism laboratory.

Dr. David Liu, CCTN, chaired a workshop entitled "Medication-assisted treatments for substance use disorders" at the 2012 Annual National Conference of the Association for Medical Education and Research in Substance Abuse (AMERSA) held November 1-3, 2012. The workshop was chosen to receive the conference's Best Workshop Award.

Dr. Samia Noursi, DCNBR and Deputy Coordinator, Women and Sex/Gender Differences Research Program was invited to attend the 2013 International Women of Courage Awards Ceremony held by the Secretary of State and hosted by the First Lady of the U.S., Michelle Obama. The 102nd Anniversary of International Women's Day was held on March 8, 2013 at the Department of State. Dr. Noursi was invited to attend this ceremony because of her service on the "White House Interagency Committee on the Implementation of the US Strategy to Prevent and Respond to Gender-Based Violence Globally." NIH is represented on this committee by the Director of ORWH, the Research Director of ORWH and Dr. Noursi.

Dr. Samia Noursi, DCNBR and Deputy Coordinator, Women and Sex/Gender Differences Research Program recently became a member of the White House Working Group on the Intersection of HIV/AIDS, Violence Against Women and Gender-related Health Disparities, established following a presidential memorandum creating this group calling for select Federal agencies to improve data collection, research, and intervention strategies related to the intersection of these issues and to improve cooperation between agencies and with external partners. Dr. Noursi represents NIDA on this committee.

Dr. Samia Noursi, DCNBR and Deputy Coordinator, Women and Sex/Gender Differences Research Program recently joined ORWH in representing NIH on the HHS Interpersonal and Domestic Violence Screening and Counseling Research Initiative. Per request from Dr. Howard Koh, Assistant Secretary for Health, a working group was established focusing on Interpersonal and Domestic Violence Screening Research. The participating agencies are ACF, ACL, ASPE, AHRQ, CDC, NIH, OASH, OPA, OWH, and SAMHSA. One of the goals of this working group is to plan for a conference in 2013 hosted by the participating agencies.

Dr. Minna Liang, OEA, will be assuming the role of OEA representative on the NIDA Genetics Coordinating Committee (NGCC). NGCC coordinates the administrative oversight of NIDA grants and supplements with human genetic components. NGCC also coordinates the NIDA Genetics Consortium Steering Committee (NGCSC) which oversees the activities of the NIDA Genetics Consortium.

Dr. Jose Ruiz, OEA, was invited to represent NIDA on the NIH-Wide SRO Technical Competencies Subcommittee, a trans-NIH committee chartered to define technical competencies, key behaviors, proficiency levels, and training for the NIH scientific review community.

Dr. Geoffrey Schoenbaum, IRP, was elected as a Fellow in the Eastern Psychological Association, and was elected into the JHU Society of Scholars.

Michele Straus and David Liu, CCTN, served as deputy coordinator and assistant coordinator, respectively, for NIDA's 2012 Combined Federal Campaign (CFC) efforts. NIDA's outstanding participation in the campaign was recognized with a Chairman's Award from the CFC of the National Capital Area (CFCNCA). NIDA's campaign team also received an award for "Best Poster or Display" (Small Agency Category) in the CFCNCA Campaign Contest.

Accreditation of the IRP Animal Research Program

The Association for the Accreditation of Laboratory Animal Care (AAALAC International) conducted its tri-annual site visit in November 2012. There was a thorough review of the IRP's animal care and use program including procedures/policies, ACUC, and physical facilities. The site visit was highly successful and the IRP was granted continued full accreditation.

Staff Changes

New Appointments/Transfers

Dr. Mark Swieter is serving as Acting Director, OEA

Stephanie Older, J.D., has been named Deputy Branch Chief, Public Information and Liaison Branch, OSPC.

Sheri Grabus, Ph.D., has been named Acting Press Officer, Public Information and Liaison Branch, OSPC.

Drs. Cora Lee Wetherington and **Samia Noursi** have recently moved from the Division of Basic Neuroscience and Behavioral Research to join the Division of Clinical Neuroscience and Behavioral Research where they will continue to advance NIDA's Women and Sex/Gender Research Program.

Lanette Palmquist transferred from SPB to PILB within OSPC.

New Employees

Kate Bent, RN, PhD, CNS, joined NIDA on February 25, 2013 as the new Deputy Director of the Office of Extramural Affairs. Before coming to NIDA, Dr. Bent was at the NIH Center for Scientific Review (CSR) where she was Senior Advisor to the Director, responsible for advising on strategic planning, budget, analysis, integration, and policy. Prior to that, she served as the Chief of CSR's Healthcare Delivery and Methodologies (HDM) Integrated Review Group. She came to NIH from the Department of Veterans Affairs central office in Washington, D.C., where she served as Scientific Program Manager for health services research in the Office of Research and Development. Previously, Dr. Bent held a clinical research position at the Denver VA Medical Center, where her work focused on transitions and caring for patients with complex chronic conditions. She held a faculty appointment at the University of Colorado Health Sciences Center, where she taught Health Policy and Applied Epidemiology. Dr. Bent, a past president of the Council on Nursing and Anthropology, has published extensively in areas of clinical research, theory, health policy, public health, and translation and implementation of research. Dr. Bent earned her Ph.D. from the University of Colorado at Denver and is an advanced practice registered nurse with specializations in complex illness and home and community health.

Gregg Friedman joined NIDA on March 11, 2013 as the new Chief Information Officer and Chief of the Information and Resource Management Branch within the Office of Management. Prior to coming to NIDA, Gregg was a Project Manager and Leader in the NIH Business System (NBS) Office where over the past 5 years he has overseen systems architecture and enterprise software delivery across the organization. Prior to that, he served as a Senior Business Consultant in the Oracle Solutions Group at BearingPoint, Inc., and provided integral expertise and leadership on the implementation and stabilization for the HHS Program Support Center's Unified Financial Management System. Gregg earned a MIS and Finance degree in Business Administration from the George Washington University, holds Project Management Professional and Contract Officer certifications, and brings over 10 years of combined experience in project management, strategic analysis, systems architecture and integration, and premier service support.

Christopher Belt joined the Office of Acquisitions' Consolidated Station Support/Simplified Acquisitions Branch as a Supervisory Contract Specialist and Branch Chief on March 11, 2013. Prior to coming to NIDA, Christopher was with the NIH Clinical Center.

Mario Gray joined the Office of Acquisitions' Consolidated Station Support/Simplified Acquisitions Branch as a Contract Specialist on February 10, 2013. Mario holds a BA with majors in Political Science and Economics. Prior to coming to NIDA he served with the Food and Drug Administration.

Nathaniel Fredericks joined NIDA's Management Analysis Branch within the Office of Management as a Management Analyst on February 24, 2013. Prior to coming to NIDA he served with the HHS Program Support Center.

William Etti joined NIDA's Management Analysis Branch within the Office of Management as a Management Analyst on February 24, 2013. William holds Master of Science in Management and Master of Business Administration degrees from the University of Maryland and has 12 years of work experience at the NIH in multiple aspects of business operations. Prior to coming to NIDA, he worked at the Clinical Center, Office of Purchasing and Contracts.

Raymond Hawkins, Jr. joined NIDA's Administrative Management Branch (AMB) under the NIDA Office of Management as a Management Analyst on March 11, 2013. Ray holds a BS in Financial Economics with a minor in Public Administration from the University of Maryland, Baltimore County (UMBC) and an MBA in Management from the University of Maryland, University College (UMUC). Prior to coming to NIDA, Ray served as the primary senior contracting officer to several NIH Office of the Director (OD) programs (e.g., NIH Business Systems Office), where he was responsible for the strategic planning, managing, oversight and justification of various contract requirements in the areas of: professional consulting support services, enterprise-wide business management solutions and information technology (IT) support systems.

Andrea McGee joined the Office of Acquisitions' Consolidated Station Support/Simplified Acquisitions Branch as a Lead Contract Specialist on April 21, 2013. Andrea holds a BA in Public Administration. Prior to coming to NIDA she worked for the Clinical Center as a Contract Specialist, Invoice Specialist and the Back-up Purchase Card Coordinator.

Dr. Mark Verdecia joined the Optogenetics and Transgenic Technology Core facility at the IRP and oversees the Protein Discovery and Engineering program.

Dr. Mark Henderson was appointed as a Research Fellow in the GNI lab at the IRP.

Departures

Dr. Meena Hiremath, OEA, left NIDA March 23, 2013 to become the Director of NHLBI's Office of Extramural Policy and Training. Meena began her career at NIDA as a Scientific Review Officer for NIDA-F, the Health Services Review Committee. She subsequently became the NIDA Receipt and Referral Officer, and in that position she was instrumental in working with NIDA colleagues to develop the referral decision tree to make referral more reliable, transparent and efficient. She also was the staff liaison for two important Council workgroups, the Diversity and Health Disparities Council Review Work Group and the Adoption of NIDA's Evidence-based Treatments in Real World Settings Work Group, where her organizational and writing skills were much appreciated by the Council workgroup members and staff.

Idella Simpson, a Contract Specialist in the Office of Acquisitions' Consolidated Station Support/Simplified Acquisitions Branch transferred to NIMH on March 23, 2013.

James Delloso, an IT Specialist in NIDA's Information Resources Management Branch within the Office of Management left NIDA on April 6, 2013 to take a position with the Department of State.

Lisa Gerring, an Extramural Support Assistant in DPMCDA resigned from her position at NIDA on April 19, 2013.

Joseph Tam Lung, a Contract Specialist in the Office of Acquisitions' Contracts Management Branch left NIDA on April 20, 2013 for a position in DHHS/ASPR.

Retirements

Susan Schlossberg retired on January 31, 2013 after 23 years of Federal service, the last 20 of which were with NIDA. Sue began her career at NIMH, transferred to ADAMHA's Office of the Administrator, and then returned to assume several positions at NIMH including Executive Assistant to the Deputy Director and later, Executive Assistant to the NIMH Acting Director. Sue came to NIDA in 1994 and has, since then, skillfully managed the day-to–day administrative operations within the Office of the Director. Over the past two decades she has also served as Staff Assistant to several NIDA Directors with resourcefulness and dedication. During her tenure at NIDA, Sue received multiple professional awards including the NIDA Director's Award in 2011, which recognized her impact on enhancing the organizational operations of the Office of the Director. In addition to the significant administrative contributions she has made while with NIDA, Sue has also used her creative talents to help promote the Institute's mission in many other ways, most notably in the design of graphics for NIDA's "Principles of Drug Abuse Treatment" booklet as well as other drug abuse treatment-related materials.

Anne Jarrett, OEA, retired from Federal service on February 28, 2013. Anne Jarrett worked at NIDA for 12 years, first within the OD and for the last 6 years in the Office of Extramural Affairs. While in OEA, she served as Program Analyst and special assistant to the Director of OEA. Anne was known for her tenacity, organizational skills, and willingness to take on new tasks, such as organizing the Certificates of Confidentiality, working with members of the Advisory Council on travel and related matters, and serving as office manager.

GRANTEE HONORS

On Tuesday, January 17, 2013, NIDA grantee **Dr. Michael Clatts** was recognized as an Honorable Professor by the Hanoi Medical University (HMU) in Vietnam. The University recognized Dr. Clatts for his efforts, through his NIDA-funded grants, to build the research capabilities of HMU in ongoing collaborations to develop and implement substance abuse and HIV/AIDS prevention interventions among persons at high risk in Hanoi and Ho Chi Minh City.

Dr. Peter W. Schiller, Director of the Laboratory of Chemical Biology and Peptide Research at the Clinical Research Institute of Montreal and a NIDA grantee, has been appointed Lee Wee Nam Visiting Professor in the School of Biological Sciences at the Nanyang Technological University (NTU) in Singapore. He will give lectures on his development of opioid compounds with novel activity profiles for use in chronic pain treatment and will engage in collaborative research with NTU on cylcotide-based opioid analgesics.

Dr. Tor Wager, University of Colorado at Boulder, was selected to receive the Cognitive Neuroscience Society's Young Investigator Award at their annual meeting held April 13-16, 2013 in San Francisco, CA.

CTN Grantee Honors:

Florida Node Alliance

Dr. Paula Riggs of the University of Colorado School of Medicine received the American Academy of Child and Adolescent Psychiatry (AACAP) Elaine Schlosser Lewis Award for Research on Attention-Deficit Disorder for her paper on adolescents receiving treatment for both ADHD and substance abuse. The study was funded by NIDA's CTN. Dr. Riggs received the award in recognition for her paper, "Randomized Controlled Trial of Osmotic-Release Methylphenidate With Cognitive-Behavioral Therapy in Adolescents With Attention-Deficit/Hyperactivity Disorder and Substance Use Disorders," published in the September 2011 issue of the *Journal of the American Academy of Child and Adolescent Psychiatry (JAACAP)*. This award information was included in the most recent issue of NIDA in the News, the internal newsletter, which is repackaged as "What's New at NIDA" – http://www.drugabuse.gov/list/2013/public029.html.

New England Consortium

Dr. Roger Weiss won the 2012 Dan Anderson Research Award for the POATS main outcome paper. This award recognizes a single published article by a researcher who has advanced the scientific knowledge of addiction treatment and recovery. Dr. Weiss earned the award for his study, "Adjunctive Counseling during Brief and Extended Buprenorphine-Naloxone Treatment for Prescription Opioid Dependence," published in 2011 in the *Archives of General Psychiatry*. Please see the full article at: http://www.hazelden.org/web/public/dananderson.page

Delaware Valley Node

Dr. George Woody, Principal Investigator of the Delaware Valley Node, has been selected for the John P. McGovern Award given annually by AMERSA. The John P. McGovern award is given to an individual who has played a significant role in substance abuse research and education. AMERSA is a national organization of researchers and educators in the field of substance abuse. He is scheduled to give the McGovern Lecture on Friday, November 8, 2013, at the AMERSA annual meeting in Bethesda, MD.

Western States Node

Dr. James Sorensen, co-director of the Western States Node and Professor of Psychiatry at the University of California, San Francisco is the recipient of The College on Problems of Drug Dependence (CPDD) Mentorship Award for 2013. CPDD is the longest-standing group in the United States addressing problems of drug dependence and abuse, and serves as an interface among governmental, industrial, and academic communities in the drug abuse field.

The Mentorship Award, established in 2000, is given annually to a member of CPDD who has been an exemplary mentor to developing researchers in the field of drug dependence. Dr. Sorensen was nominated by several of his current and former fellows. Dr. Sorensen has trained 15 faculty members, 28 post-doctoral fellows, and 22 pre-doctoral fellows. He is the director of a T32 training grant funded by the National Institute on Drug Abuse, the Research Training Core director in UCSF's Drug Abuse Treatment and Services Research Center, cluster leader of the Clinical Psychology Training Program for pre-doctoral and post-doctoral fellows, and co-director of the Visiting Professors Program at the Center for AIDS Prevention Studies (CAPS) at UCSF. Dr. Sorensen will receive the award at CPDD's 75th Annual Meeting in San Diego, California, June 15-20, 2013.

Appalachian Tri-State Node

Antoine Douaihy, M.D. has been chosen by the current student members of the University of Pittsburgh School of Medicine to receive the Charles Watson Teaching Award. The Charles Watson Teaching Award recognizes a faculty clinician who best embodies the qualities of Dr. Charles Watson - a masterful clinician, academician, caretaker of his patients, educator, mentor, and contributor to the medical school community and community at large. Dr. Douaihy is considered an outstanding educator who consistently receives teaching awards from medical students, psychiatric residents and others. No one has promoted the use of motivational interviewing, medication-assisted-treatments for addiction, and other evidenced-based therapies to physicians, students, residents and fellows as much as he has within the School of Medicine. This award will be presented at the ***Alpha Omega Alpha*** (AOA) Honor Medical Society Induction Banquet on April 23, 2013.